1 TITLE

CLINICAL STUDY PROTOCOL

STUDY TITLE:	A Phase 3, Randomized, Double-Blind, Placebo Controlled Study of the Efficacy and Safety of Roxadustat (FG-4592) for the Treatment of Anemia in Chronic Kidney Disease Patients not on Dialysis
PROTOCOL NUMBER:	FGCL-4592-060
SPONSOR:	FibroGen, Inc. 409 Illinois Street San Francisco, California 94158 USA
IND NUMBER:	74,454
STUDY DRUG:	Roxadustat (FG-4592)
INDICATION:	Anemia associated with chronic kidney disease
FIBROGEN MEDICAL MONITOR	Name: [redacted] Title: [redacted] Telephone: [redacted] Mobile/Pager: [redacted] E-mail Address: [redacted]
ORIGINAL PROTOCOL DATE:	08 September 2012
PROTOCOL VERSION & DATE:	Amendment 1: 14 January 2014 Amendment 2: 10 October 2014 Amendment 3: 20 September 2017

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INVESTIGATOR SIGNATURE PAGE

STUDY ACKNOWLEDGEMENT

A Phase 3, Randomized, Double-Blind, Placebo Controlled Study of the Efficacy and Safety of Roxadustat (FG-4592) for the Treatment of Anemia in Chronic Kidney Disease Patients not on Dialysis

FGCL-4592-060

Amendment 3

20 September 2017

INVESTIGATOR STATEMENT

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

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

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

Investigator Name (Printed)	Institution
Signature	Date

Please retain the original for your study files.

SUMMARY OF MAJOR PROTOCOL AMENDMENT CHANGES

Amendment 3

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

Description of Change	Rationale for Change	Section(s) Affected [a]
The treatment Period for subjects enrolled has been clarified. It now reads as follows (added text is italicized): Treatment Period: Variable for individual subjects, with a minimum treatment duration of 52 weeks and a maximum treatment duration of time to enroll all subjects plus 52 weeks after the last subject is randomized • The last subject randomized will complete 52 weeks of treatment • All subjects randomized in the trial will continue treatment for 52 weeks after the final subject is randomized ***Amendment 3*** *Treatment duration is variable for individual subjects. In order to complete the Treatment Period simultaneously for all study subjects, the minimum treatment duration may be less than 52 weeks, with a maximum treatment duration of up to 3 years after the last subject is randomized.*	This study is part of a phase 3 program whose completion is event driven. This amendment will allow this study to continue so that it can contribute to the larger program's objectives	Synopsis, Sections 4.1, 4.5.1 and 7.1.2

Description of Change	Rationale for Change	Section(s) Affected [a]
Protocol Deviation: *Text has been added to pre-specify issues that are not considered protocol deviations.* *Added text reads as follows:* *A protocol deviation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol and must protect the rights, safety, and welfare of subjects. The investigator should not implement any deviation from, or changes to, the protocol, unless it is necessary to eliminate an immediate hazard to study subjects.* *Due to the complex study design and standard of clinical practice, the following issues should not be captured and reported as protocol deviations.* *Given the complexities of the dose adjustment algorithm, and the need to take into consideration various clinical parameters, it is not considered a protocol deviation when study subjects are dosed based on their clinical circumstance, whether or not this is concordant with the roxadustat dosing algorithm,* ***unless*** *it is related to "excessive hematopoiesis" (refer to Section 4.5.1) or "Overdose" (prescribed >3.0 mg/kg per dose).* *ESA administration in during hospitalization: Such ESA use is not considered a protocol deviation, if study subjects have no access to study drug while hospitalized.* .	This section was added to align the protocol with a new SOP for protocol templates. Specifically: Various factors, such as discrepancies between HemoCue Hb and Central lab Hb value, Investigator decision etc. can influence dose titration decisions at the time of the visit or after the visit. As a result, the dose prescribed may not exactly match the dose per the dose adjustment algorithm. However, as the stable dose would be achieved through titration, dosing discrepancy when subjects are dosed based on their clinical status is not considered a protocol deviation unless it is related to excessive hematopoiesis (≥13.0 g/dL, requires a dose-hold) or overdose (>3.0 mg/kg/dose). Roxadustat subjects may receive ESA while hospitalized, in part due to lack of access to roxadustat while in hospital, and/or as part of hospital standard-of-care of anemia treatment; therefore, ESA administration in such circumstances is not considered a protocol deviation.	Section 9.5.1

Description of Change	Rationale for Change	Section(s) Affected [a]
Statistical Analysis Changes: 1) Primary analysis model is changed from MMRM to MI ANCOVA 2) One secondary endpoint is removed 3) Minor wording changes to secondary endpoints analyses	1) Based on FDA feedback 2) One secondary endpoint is no longer relevant due to variable duration of treatment in the study 3) Bring more clarity to the model specifications	Synopsis, Sections 9.4.3.1, 9.4.3.2, and 9.4.3.3

]Abbreviations: AE = adverse event; BIW = twice a week; BP = blood pressure; CPK = creatine phosphokinase; CSE = cardiac safety events; CV = cardiovascular; CTCAE = Common Terminology Criteria for Adverse Events; DVT = deep vein thrombosis; ECG = electrocardiogram; EMA = European Medicines Agency; EOS = end of study; EPO = erythropoietin; ESA = erythropoiesis stimulating agent; ET = early termination; FDA = US Food and Drug Administration; Hb = hemoglobin; HMG-CoA = hydroxymethylglutaryl coenzyme A; IV = intravenous; MACE = major adverse cardiac event; N = total number of subjects; NCI = National Cancer Institute; PE = pulmonary embolism; QoL = quality of life; QW = once weekly; SAP = Statistical Analysis Plan; SmPC = Summary of Product Characteristics; TSAT = transferrin saturation; USPI = United States Package Insert; VAT = vascular access thromboses.

a Primary sections listed only; other sections may have been updated accordingly.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
BIW	twice weekly
BP	blood pressure
CBC	complete blood count
CFB	change from baseline
CFR	Code of Federal Regulations
CHOIR	Correction of Hemoglobin and Outcomes in Renal Insufficiency study
CHr	reticulocyte hemoglobin content
CKD	chronic kidney disease
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CRP	C-reactive protein
CS	clinically significant
DSMB	Data and Safety Monitoring Board
DVT	deep vein thrombosis
EC	Ethics committee
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOS	End of Study
EPO	erythropoietin
EQ-5D-5L	European Quality Of Life questionnaire in Five dimensions, Five levels
ESA	erythropoiesis-stimulating agent
ESRD	end-stage renal disease
EOT	End of Treatment
ET	Early Termination (visit)
FACT-An	Functional Assessment of Cancer Therapy – Anemia
FAS	Full Analysis Set

Abbreviation	Definition
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
Hb	hemoglobin
HbA1C	hemoglobin A1c
HbsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HDPE	high-density polyethylene
HDL	high-density lipoprotein
HIF	hypoxia-inducible factor
HIF-PH	hypoxia-inducible factor prolyl hydroxylase
HIF-PHI	hypoxia-inducible factor prolyl hydroxylase inhibitor
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	heart rate
HRQoL	Health-Related Quality of Life
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	international normalized ratio
IRB	Institutional Review Board
ITT	Intent to Treat
IV	intravenous
IWRS	Interactive or Web Response System)
KDOQI	Kidney Disease Outcomes Quality Initiative
LDL	low-density lipoprotein
LFT	liver function test
LLN	lower limit of normal
LOCF	last observation carried forward
MAP	mean arterial pressure

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities
MDRD	Modification of diet in renal disease equation
MI	myocardial infarction
MI ANCOVA	multiple imputation analysis of covariance
MMRM	mixed model of repeated measures
N (or n)	sample size
NCS	not clinically significant
NKF	National Kidney Foundation
PCS	potentially clinically significant
PE	pulmonary embolism
PEY	patient-exposure-year
PF	physical Functioning subscale component of SF-36
PH	Prolyl hydroxylase
PPS	Per Protocol Set
PR	In an ECG, the interval between the P wave and the beginning of the QRS wave complex)
PK	pharmacokinetics
QoL	Quality of Life
QRS	Q wave, R wave, and S wave complex in an ECG
QT	In an ECG, the interval between the start of the Q wave and the end of the T wave
QTc	QT interval corrected for heart rate
QW	once weekly
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
SF-36	The 36-Item Short Form Health Survey
SOC	system organ class
Subcut	subcutaneous
sTfR	soluble transferrin receptor
Tbili	total bilirubin
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TIBC	total iron binding capacity

Abbreviation	Definition
TIW	three times weekly
TSAT	transferrin saturation
ULN	upper limit of normal
USRDS	United States Renal Data System
VAT	vascular access thrombosis
VEGF	vascular endothelial growth factor
VHL	Von Hippel-Lindau
WBC	white blood cell
WHO Drug	World Health Organization Drug

PROTOCOL SYNOPSIS

Study Title:	A Phase 3, Randomized, Double-Blind, Placebo Controlled Study of the Efficacy and Safety of Roxadustat (FG-4592) for the Treatment of Anemia in Chronic Kidney Disease Patients not on Dialysis
Protocol Number:	FGCL-4592-060
Investigational Product:	FG-4592
Target Population:	Anemic Stage 3, 4, or 5 chronic kidney disease (CKD) subjects
IND Number:	74,454
Study Phase:	Phase 3
Study Centers Planned:	Up to approximately 200 study centers worldwide
Number of Subjects Planned:	Up to 1200 planned subjects will be randomized in a 2:1 ratio to receive either roxadustat (approximately 800 subjects) or placebo (approximately 400 subjects) in a double-blind manner.
Primary objectives:	• Evaluate the efficacy of roxadustat for the treatment of anemia (correction and maintenance of hemoglobin [Hb]) in CKD subjects not on dialysis. • Evaluate the safety of roxadustat administered over a minimum of 52 weeks of treatment.
Secondary objectives:	• Evaluate the effect of roxadustat on serum lipid parameters • Evaluate the effect of roxadustat on health-related quality of life (HRQoL) • Evaluate the effect of roxadustat on blood pressure (BP) • Evaluate the need for anemia rescue therapy: red blood cell (RBC) transfusion, erythropoiesis-stimulating agent (ESA), or intravenous (IV) iron • Evaluate time to achieve Hb response
Study Design:	This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study in anemic subjects with Stage 3, 4, or 5 CKD who are not on dialysis. This study will consist of three study periods: • **Screening Period:** Up to 6 weeks

	• **Treatment Period:** Treatment duration is variable for individual subjects. In order to complete the Treatment Period simultaneously for all study subjects, the minimum treatment duration may be less than 52 weeks, with a maximum treatment duration of up to3 years after the last subject is randomized. • **Post-Treatment Follow-Up Period*:** 4 weeks (*or enroll into an Open Label Extension study) Following the Screening Period, subjects will be randomized in a 2:1 ratio to receive either roxadustat or placebo. Stratification factors include screening Hb values, cardiac/cerebrovascular/thromboembolic medical history, estimated glomerular filtration rate (eGFR), and geographic region. The Investigator, study site staff, subject, and the Sponsor, are blinded to study drug assignment, but not to dose level. Additionally, all efforts should be made to keep subjects blinded to study Hb values. Dosing will be three times weekly (TIW) throughout the study, except in subjects who have already converted to twice a week (BIW) or once a week (QW) dosing regimens under previous FGCL-4592-060 protocol versions. Starting doses of study drug will be dose-adjusted according to anemia correction guidelines until subjects achieve a Hb value of ≥ 11 g/dL and ≥ 1 g/dL increase from baseline, by central lab. Once these criteria are met subjects will enter the maintenance phase of anemia treatment and will be dose-adjusted according to maintenance guidelines (Section 2.1 and Appendix 1). **Scheduled Visits During Treatment** During the Treatment Period, subjects will attend consecutive weekly study visits for the first 2 weeks of study treatment (from Weeks 0 to 2) followed by every other week study visits starting at Week 4 through Week 24. After Week 24, subjects will attend study visits every 4 weeks until the End of Treatment (EOT) Period (Week 28 to EOT). Treatment duration is variable for individual subjects. In order to complete the Treatment Period simultaneously for all study subjects, the minimum treatment duration may be less than 52 weeks, with a maximum treatment duration of up to 3 years after the last subject is randomized. After the Treatment Period, study subjects may enter a separate Open Label Extension Study or will proceed to the 4-week post-treatment Follow-up Period and will attend a final study visit at 4 weeks after EOT. Subjects who prematurely discontinue study treatment will complete the Early Termination (ET) and End of Study (EOS)

visits. Such a subject will be considered a non-completer of treatment and/or the study. However, these subjects will continue to be followed-up for vital status, safety events requiring potential adjudication, as well as important concomitant medication use (eg, ESA), at periodic intervals of 3 to 6 months until the end of the overall study unless the subject withdraws consent for this modified follow-up.

Starting Dose of Study Drug:

The initial study drug dose (per dose amount) is based on a tiered, weight-based dosing scheme shown in Table S1.

Table S1. Initial Study Drug (Roxadustat or Placebo) Dosing (TIW)

Tiered Weight Category	(<70 kg)	(≥70 kg)
Initial Tiered Weight Dose (TIW)	70 mg	100 mg

Abbreviations: TIW = three times weekly.

Study drug dose will remain constant during the first 4 weeks of the Treatment Period, unless a dose reduction is required for excessive hematopoiesis. Dose adjustments are permitted starting at Week 4, and at intervals of every 4 weeks thereafter. In contrast, dose frequency conversions may occur at any dosing week (even before Week 4), if the criteria for dose frequency conversion are met as described in Section 4.5.2.

Correction Phase of Dosing

The aim of the Correction Phase is to increase Hb from baseline to a level that avoids the need for blood transfusion, using the dosing algorithm presented in Appendix 1, and taking into account physiologic fluctuations and test variability. This phase is variable in length for each subject, depending on when the subject achieves a Hb level ≥ 11.0 g/dL and ≥ 1.0 g/dL increase from baseline by central lab.

Maintenance Phase of Dosing

The aim of the Maintenance Phase is to maintain Hb levels after the initial correction, utilizing the dosing algorithm described in Appendix 1, and taking into account physiologic fluctuations and test variability.

Supplemental Iron Use

Oral iron is recommended for dietary supplementation to support erythropoiesis and as the first-line for prevention and treatment of iron deficiency, unless the patient is intolerant to this route of

	treatment. The recommended daily oral dose for the treatment of iron deficiency is 200 mg of elemental iron. IV iron is restricted as rescue therapy, using the Rescue Therapy Guidelines below. **Rescue Therapy Guidelines** Rescue therapy guidelines are provided to standardize the use of rescue therapy and to ensure safety of study subjects. • *Red Blood Cell Transfusion* Red blood cell (RBC) transfusion is allowed if rapid correction of anemia is required to stabilize the patient's condition (eg, acute hemorrhage) or the Investigator is of the opinion that the blood transfusion is a medical necessity. Study drug treatment may continue during or after RBC transfusion administration. • *Erythropoiesis-Stimulating Agent (ESA)* Use of *more than two* courses of an ESA for anemia rescue is a withdrawal criterion requiring early termination from study treatment. Nevertheless, criteria for use of ESA are provided in order to standardize the use of ESA rescue. The Investigator should consider initiating the use of an approved ESA only if all of the following criteria are met: • The subject's Hb level has not sufficiently responded to two or more dose increases or maximum doses (by body weight) of study drug; **and** • The subject's Hb is < 8.0 g/dL; **and** • Reducing the risk of alloimmunization in transplant eligible subjects and/or reduction of other RBC transfusion-related risks is a goal The subject is not allowed to be administered both ESA and study drug at the same time. ESA treatment must be stopped after 4 weeks of use or when Hb ≥ 9 g/dL is reached, whichever occurs first. Study drug treatment may be resumed after the following intervals: • Two days after stopping epoetin • One week after stopping darbepoetin alfa • Two weeks after stopping methoxy polyethylene glycol-epoetin beta (Mircera®) After two successful courses of rescue with ESA and return to study drug, subjects who again meet the above criteria for ESA rescue and receive a third course of ESA must be discontinued from the study drug at this point. Such a subject will complete procedures for early termination and subsequent modified follow-

	up according to the procedures outlined in Section 7.1.2.6, if consent is not withdrawn to do so. • *Intravenous Iron* The use of intravenous iron is discouraged in the setting of this placebo-controlled trial. In roxadustat phase 2 studies where IV iron was restricted, iron repletion was not required for treatment of anemia. IV iron is not standard of care in CKD nondialysis patients in most regions of the world. Therefore, the subject may receive IV iron supplementation only if each of the following criteria are met: • The subject's Hb has not responded adequately to two or more dose increases or the maximum dose (by body weight) of study drug; **and** • The subject is unresponsive to or does not tolerate oral iron; **and** • Ferritin levels are < 100 ng/mL (< 220 pmol/L) **OR** TSAT is < 20% If IV iron rescue criteria are met, the dose in a single administration (day) should me no more than 250 mg. The selection and dosing of the IV iron formulation should be consistent with regional package inserts that are applicable to CKD-ND patients. Study drug treatment may continue during IV iron administration. At 4-8 weeks after the single dose of IV iron, a repeat dose of IV iron can be administered if the Hb remains < 9 g/dL AND the subject still meets iron deficiency criteria (ferritin < 100 ng/mL(< 220 pmol/L) or TSAT < 20%). After this 8-week period, full IV iron rescue criteria would need to be met again in order to qualify a subject for a second course of IV iron at a later point in the trial. **Therapeutic Phlebotomy** If there are clinical concerns due to excessive elevation in Hb levels, the Investigator may decide to perform a therapeutic phlebotomy instead of, or in addition to, a dose hold; this should be documented and discussed with the study Medical Monitor.
Inclusion Criteria	1. Age ≥ 18 years 2. Subject has been informed of the investigational nature of this study and has given written informed consent in accordance with institutional, local, and national guidelines 3. Diagnosis of CKD, with Kidney Disease Outcomes Quality Initiative (KDOQI) Stage 3, 4, or 5, not receiving dialysis; with

	an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 estimated using the abbreviated 4-variable Modification of Diet in Renal Disease (MDRD) equation 4. Mean of the three most recent Hb values during the Screening Period, obtained at least 4 days apart, must be ≤ 10.0 g/dL, with a difference of ≤ 1.0 g/dL between the highest and the lowest values. The last screening Hb value must be within 10 days prior to randomization 5. Ferritin ≥ 30 ng/mL (≥ 66 pmol/L) 6. TSAT > 5% 7. Serum folate level ≥ lower limit of normal (LLN) 8. Serum vitamin B_{12} level ≥ LLN 9. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 x upper limit of normal (ULN), and total bilirubin (Tbili) ≤ 1.5 x ULN 10. Body weight 45 to 160 kg
Exclusion Criteria:	1. Any ESA treatment within 12 weeks prior to randomization 2. More than one dose of IV iron within 12 weeks prior to randomization 3. RBC transfusion within 8 weeks prior to randomization 4. Active, clinically significant infection that could be manifested by white blood cell (WBC) count > ULN, and/or fever, in conjunction with clinical signs or symptoms of infection 5. History of chronic liver disease (eg, chronic infectious hepatitis, chronic auto-immune liver disease, cirrhosis, or fibrosis of the liver) 6. New York Heart Association Class III or IV congestive heart failure 7. Myocardial infarction, acute coronary syndrome, stroke, seizure, or a thromboembolic event (eg, deep vein thrombosis or pulmonary embolism) within 12 weeks prior to randomization 8. Systolic BP ≥ 160 mmHg or diastolic BP ≥ 95 mmHg (confirmed by repeat measurement) within 2 weeks prior to randomization 9. Diagnosis or suspicion (eg, complex kidney cyst of Bosniak Category 2F or higher) of renal cell carcinoma on renal ultrasound within 12 weeks prior to randomization 10. History of malignancy, exceptions made for the following malignancies: a) those determined to be cured or in remission

	for ≥ 5 years, b) curatively resected basal cell or squamous cell skin cancers, c) cervical cancer in situ, or resected colonic polyps 11. Positive for any of the following: human immunodeficiency virus (HIV); hepatitis B surface antigen (HBsAg); or antihepatitis C virus antibody (anti-HCV Ab) 12. Chronic inflammatory disease that could impact erythropoiesis or is determined to be the principal cause of anemia (eg, systemic lupus erythematosus, rheumatoid arthritis, celiac disease) even if it is currently in remission 13. Known untreated proliferative diabetic retinopathy, diabetic macular edema, macular degeneration and retinal vein occlusion 14. Known history of myelodysplastic syndrome or multiple myeloma 15. Known hereditary hematologic disease such as clinically apparent thalassemia or sickle cell anemia, pure red cell aplasia, or other known causes for anemia other than CKD 16. Known hemosiderosis, hemochromatosis, coagulation disorder, or hypercoagulable condition 17. Any prior organ transplant (that has not been explanted), or a scheduled organ transplantation 18. Anticipated elective surgery that is expected to lead to significant blood loss, or anticipated elective coronary revascularization 19. Known active or chronic gastrointestinal bleeding 20. Any prior treatment with roxadustat or a hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) 21. Use of iron-chelating agents within 4 weeks prior to randomization 22. Use of an investigational drug or treatment, participation in an investigational study, or presence of expected carryover effect of an investigational treatment, within 4 weeks prior to randomization 23. Anticipated use of dapsone or androgens in any dose amount or anticipated chronic use of acetaminophen or paracetamol > 2.0 g/day during the treatment or follow-up periods of the study 24. History of alcohol or drug abuse within 2 years prior to randomization

	25. Females of childbearing potential, unless using contraception as detailed in the protocol, or sexual abstinence; male subjects with sexual partners of childbearing potential who are not on birth control unless the male subject agrees to use contraception or sexual abstinence 26. Pregnant or breastfeeding females 27. Any medical condition that in the opinion of the Investigator may pose a safety risk to a subject in this study, which may confound efficacy or safety assessment, or may interfere with study participation
Study Procedures	See Schedule of Assessments (Appendix 2)
Investigational Product, Dose, and Mode of Administration	20, 50, and 100 mg roxadustat tablets for oral administration ***Initial Doses*** Subjects will receive tiered, weight-based initial doses (Table S1). ***Dose Adjustment*** Refer to Section 2.1 and Appendix 1.
Reference Therapy (Placebo), Dose, and Mode of Administration	20, 50, and 100 mg matching placebo tablets for oral administration (control group) ***Initial Doses*** Subjects will receive tiered, weight-based initial doses (Table S1). ***Dose Adjustment*** Refer to Section 2.1 and Appendix 1.
Efficacy Endpoints and Assessments	***Primary*** The primary efficacy endpoint in this study will depend on whether the data are being filed to support submission to the US (FDA) or to Ex-US Health Authorities. • For US (FDA) submission: The change in Hb from baseline to the average level during the evaluation period ,defined as Week 28 until Week 52 • For Ex-US submission: The proportion of subjects who achieve a Hb response at two consecutive visits during the first 24 weeks of treatment, without rescue therapy A Hb response is defined, using central laboratory values, as the following: • Hb ≥ 11 g/dL and Hb increase from baseline by ≥ 1 g/dL in subjects with baseline Hb > 8 g/dL, or • Increase in Hb by ≥ 2 g/dL in subjects with baseline Hb ≤ 8.0 g/dL

	Rescue therapy is defined as RBC transfusion, ESA, or IV iron use ***Secondary*** The secondary efficacy endpoints in this study are: • For Ex-US submission only: Hb maintenance: Mean change from baseline (CFB) in Hb averaged over 8 weeks of treatment at Weeks 28 to 36, without rescue therapy within 6 weeks prior to and during this 8-week evaluation period • Mean CFB in low-density lipoprotein (LDL) cholesterol averaged over Weeks 12 to 28 • Mean CFB in the 36-Item Short Form Health Survey (SF-36) Physical Functioning (PF) subscore averaged over Weeks 12 to 28 in the Intent to Treat (ITT) subjects with baseline PF subscore below 35 • Mean CFB in SF-36 Vitality subscore averaged over Weeks 12 to 28 in ITT subjects with baseline vitality subscore below 50 • Blood pressure effect a. Mean CFB in mean arterial pressure (MAP) averaged over Weeks 20 to 28, measured as the mean of the triplicate measurements 5 minutes apart b. Time to (and proportion of subjects with) worsened hypertension (defined as systolic BP > 170 mmHg or diastolic BP > 110 mmHg measured, and an increase from baseline of ≥ 20 mmHg [systolic BP] or ≥ 15 mmHg [diastolic BP] confirmed by the mean of triplicate measurements 5 minutes apart) • Time to (and proportion of subjects who received) rescue therapy (composite of RBC transfusion, ESA use, and IV iron) in the first 24 weeks of treatment • Time to (and proportion of subjects who received) rescue therapy (composite of RBC transfusion, ESA use, and IV iron) in the first 52 weeks of treatment
Safety Assessments:	*Study-specific* safety will be assessed by evaluating the following: • Adverse events (AEs), serious adverse events (SAEs), and clinically significant changes in laboratory values from baseline • Vital signs, electrocardiogram (ECG) parameters, and clinical laboratory values *Pooled* safety interpretation will also be determined based on analyses of composite endpoints derived from adjudicated events pooled across multiple studies in the roxadustat Phase 3 program. The members of an independent adjudication committee blinded to

	treatment assignment will adjudicate the following events in multiple phase 3 studies: All cause death, myocardial infarction (MI), stroke, congestive heart failure requiring hospitalization, unstable angina requiring hospitalization, hypertensive emergency, deep venous thrombosis, pulmonary embolism, and vascular access thrombosis. Various region-specific pooled analyses of composites of these adjudicated events, pooled across multiple studies, will be conducted. The analyses of the adjudicated events will be detailed in the region-specific pooled Statistical Analysis Plan (SAP). • *For US (FDA) Only: The primary safety endpoint in this study is the MACE (Major Adverse Cardiac Event) composite endpoint, defined as time to first occurrence of death from all causes, MI, or stroke, only for the purpose of being pooled across multiple similar studies in the Phase 3 program. None of the individual studies are powered to meet the MACE primary safety endpoint individually. The pooled MACE analysis is only for purposes of supporting a US FDA regulatory filing of roxadustat.* • The above adjudicated safety events may also be used to support the pooled analyses of additional composite safety endpoints across multiple studies in the Phase 3 program, such as MACE+ (death, MI, stroke, congestive heart failure requiring hospitalization, and unstable angina requiring hospitalization), or a composite which consists of all of the adjudicated events.
Statistical Methods:	***Sample Size Determination*** The study is sufficiently powered for both primary efficacy endpoints. A minimum of 450 subjects are planned to be randomized to receive roxadustat or placebo (2:1 with approximately 300 subjects randomized to receive roxadustat versus 150 subjects randomized to receive placebo) in a double-blind manner in order to support the primary endpoint(s) of the study. **For US (FDA) Submission Primary Efficacy Endpoint** A sample size of 450 will have > 99% power to detect a 1 g/dL difference in mean Hb values between the two treatment groups, assuming that the common standard deviation is 1.2 g/dL, using an analysis of variance (ANOVA) test with a 0.05 two-sided significance level. For comparisons of individual treatment arms versus pooled placebo, a sample size of 35 roxadustat and 150 placebo will have 90% power to detect a 0.75 g/dL difference in mean Hb values

	between the two treatment groups, assuming that the common standard deviation is 1.2 g/dL, using an ANOVA test with a 0.05 two-sided significance level. **For Ex-US Submission Primary Efficacy Endpoint** Based on a two-sided test at the alpha = 0.05 level of significance, the study will have > 95% power to demonstrate a statistically significant difference between roxadustat and placebo, assuming that the proportion of subjects with a Hb response in the roxadustat group is at least 65% and the proportion of subjects with a Hb response in the placebo group is at most 25%. During the course of this Phase 3 study, which is being conducted in parallel with other Phase 3 studies, up to 1200 subjects may be enrolled in this study to support the overall safety evaluation of roxadustat across pooled comparable studies in the Phase 3 program, using adjudicated composite safety endpoints of interest. The study will stop enrollment at the Sponsor's discretion, if: 1) the minimum of 450 subjects has been achieved to support the primary efficacy endpoint in this study, and 2) sufficient adjudicated safety events have been accumulated across the nondialysis Phase 3 program to support a pooled analysis of composite safety events across multiple studies in the same population. ***Statistical Analysis*** Intent-to-Treat (ITT): All randomized subjects. Safety Population: All subjects who receive any dose of study drug. Per Protocol Set (PPS): All randomized subjects who receive at least 12 weeks of study treatment, have valid corresponding Hb measurements, and are without major protocol violations. Full criteria to be defined in the SAP. All primary and secondary efficacy analyses will be based on the ITT population. The PPS population will be utilized for supportive analysis of primary and secondary endpoints. Laboratory values from the central laboratory will be used for all analyses. The baseline Hb value for efficacy analyses is defined as the mean of four central laboratory Hb values: the last three screening Hb values prior to randomization plus the predose Hb value on Day 1 of the Treatment Period. Hemoglobin values after a rescue therapy will not be excluded for the FDA primary efficacy analysis. Hemoglobin values within 6 weeks after a rescue therapy will be excluded for the Ex-US primary efficacy endpoint as well as other sensitivity efficacy analyses. The Mixed Model with

	Repeated Measures (MMRM) model will be used for missing data imputation in the primary analyses. The primary efficacy endpoint for the US (FDA) submission will be analyzed using the MI ANCOVA model comparing Hb CFB to the average of Weeks 28 to 52, stratified by the baseline value and randomization stratification factors, in a fixed sequence procedure: 1) pooled roxadustat (TIW+BIW+QW) vs. pooled placebo, 2) roxadustat TIW vs. pooled placebo, 3) roxadustat BIW vs. pooled placebo, 4) roxadustat QW vs. pooled placebo. The latter are being performed to test the BIW and QW maintenance dosing frequencies that are enrolled from earlier versions of the protocol. If a null hypothesis is rejected, the claim of the tested roxadustat regimen over placebo will be declared successful and the test will progress to the next comparison in sequence. The model will contain terms for treatment arm, baseline measurement, visit, visit x treatment arm, and other stratification factors. The primary efficacy analysis will be based on the estimated difference in the overall mean effect between the two treatment groups throughout the evaluation period based on the MI ANCOVA model. The hypothesis to be tested for the primary efficacy analysis is: H_0: Hb CFB to the average of Weeks 28 to 52 in the roxadustat group = Hb CFB to the average of Weeks 28 to 52 in the placebo group Versus H_1: Hb CFB to the average of Weeks 28 to 52 in the roxadustat group ≠ Hb CFB to the average of Weeks 28 to 52 in the placebo group H_0 will be tested at the two-sided alpha=0.05 level of significance and will be rejected if the $p < 0.05$ from the test. The primary efficacy endpoint for the Ex-US submission will be analyzed using the Cochran-Mantel-Haenszel (CMH) test comparing pooled roxadustat (TIW+BIW+QW) to pooled Placebo (TIW+BIW+QW) stratified by the randomization stratification factors. The hypothesis to be tested for the primary efficacy analysis is: H_0: Hb responder rate in the roxadustat group = Hb responder rate in the placebo group Versus H_1: Hb responder rate in the roxadustat group ≠ Hb responder rate in the placebo group H_0 will be tested at the two-sided alpha = 0.05 level of significance and will be rejected if the $p < 0.05$ from the test.

	Secondary endpoints will be tested using a fixed sequence procedure to adjust for multiple endpoints compared between the pooled roxadustat group vs. pooled placebo, followed by roxadustat TIW vs. pooled placebo. If a null hypothesis is rejected, the claim of roxadustat over placebo will be declared successful and the test will progress to the next comparison in sequence. The secondary endpoints of Hb maintenance will be analyzed using the MMRM model with baseline Hb as covariate and other randomization stratification factors as fixed effects. Missing values will be handled with the MMRM model. The test for these endpoints will compare the pooled roxadustat group (TIW+BIW+QW) to pooled placebo, followed by roxadustat TIW to pooled placebo in a fixed sequence procedure. Separately, pairwise comparisons of roxadustat (2A, 1A) to pooled placebo (1P+2P+3P) will also be performed as exploratory analyses of the BIW and QW maintenance dosing frequencies (from the original and amendment 1 versions of the protocol). The secondary analyses of mean CFB in LDL cholesterol, SF-36 PF subscore, SF-36 Vitality, and MAP will use MMRM models using baseline value as covariate and randomization stratification factors as fixed effects. Time to (and proportion of subjects with) protocol-defined worsened hypertension for the roxadustat group versus pooled placebo will be analyzed using the Cox Proportional Hazards model stratified by the randomization stratification factors. A hazard ratio and its associated 95% confidence interval (CI) will be computed to compare between the roxadustat TIW treatment group and pooled placebo. Noninferiority will be declared if the upper bound of the 2-sided 95% CI of the hazard ratio does not exceed 1.3, superiority will be declared if the upper bound of the 2-sided 95% CI of the hazard ratio does not exceed 1. Time to (and proportion of subjects with) rescue therapy over the first 24 and 52 weeks of treatment will be analyzed using the same method as outlined above. All subjects who have received any dose of study treatment will be included in the safety analyses. Safety parameters including AEs, laboratory parameters, vital signs, and ECG parameters will be tabulated using descriptive statistics. The analytical methods for the composite safety endpoints of interest will be described in a region-specific pooled SAP to reflect the nature of the pooling of these endpoints across multiple studies in the Phase 3 program and the region-specific safety endpoints.

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.

2 BACKGROUND

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

2.1 Introduction Epidemiology of CKD and ESRD

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

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

2.2 Anemia Associated with Chronic Kidney Disease

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

Anemia may present in early stages of CKD and its prevalence increases as CKD progresses. Anemia is present in 17% of patients with late Stage 3 disease; this increases to 25% in patients with Stage 4 disease, and to 49% in patients with Stage 5 CKD who have not yet progressed to dialysis (Coresh, 2007; Go, 2004). Over 90 % of patients undergoing dialysis are anemic. Half of new dialysis patients (50.1%) have hemoglobin (Hb) levels below 10 g/dL and approximately 28% have Hb below 9 g/dL (USRDS, 2003, Ch 3, Figure 3.11).

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

Anemia contributes to the excess morbidity and mortality in CKD and ESRD. In patients with CKD, the severity of anemia correlates directly with the risk of hospitalization, cardiovascular disease, and death (Collins, 1998). Patients with the lowest Hb have worse outcomes, as was discussed in the post hoc analysis of mortality by Hb quintiles for the Normal Hematocrit and Correction of Hb and Outcomes in Renal Insufficiency (CHOIR) studies in the FDA briefing document for the October 2007 Cardiovascular and Renal Advisory Committee (Unger, 2007).

Similar observations are found in USRDS mortality data stratified by Hb. All-cause mortality stratified by Hb (1993-1996) showed significantly higher first-year death rates in patients with Hb levels < 9, compared with 11 to 12 g/dL. This trend continued to worsen, as reflected in 1998 to 1999 data, where the death rate rose by ~75% compared with the 1993 to 1996 period [(USRDS, 2000), Ch 8, Fig 8.16; (USRDS,USRDS), Ch 9, Fig 9.14]. This increase coincides with the introduction of the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines in 1997. The relative risk of all-cause mortality for patients with Hb < 9 g/dL is twice that of patients with Hb > 12 g/dL [(USRDS, 2002); Ch 9, Table 9b)]. The relative risk of cardiovascular hospitalization increases significantly to 1.26 in patients with Hb levels < 9 g/dL compared with those with Hb levels at 11 to 12 g/dL [(USRDS,USRDS) Ch 5, Fig 5.27)].

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

2.3 Treatment of Anemia

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

Although the treatment of anemia in CKD and ESRD is thought to provide a quality of life (QoL) benefit, several studies in ESRD and CKD nondialysis patients have shown higher mortality or trends in that direction in the higher-dosed ESA-treated cohorts when the protocol objective was to treat to high target Hb levels (Besarab, 1998; Drueke, 2006; Singh, 2006).

An ESA dose relationship to mortality has been reported in a review of the USRDS database (Zhang, 2004) of ESRD patients who received higher ESA doses. Additionally, ESA therapy for anemia in ESRD patients on hemodialysis (HD) usually requires concomitant intravenous (intravenous [IV]) iron supplementation.

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

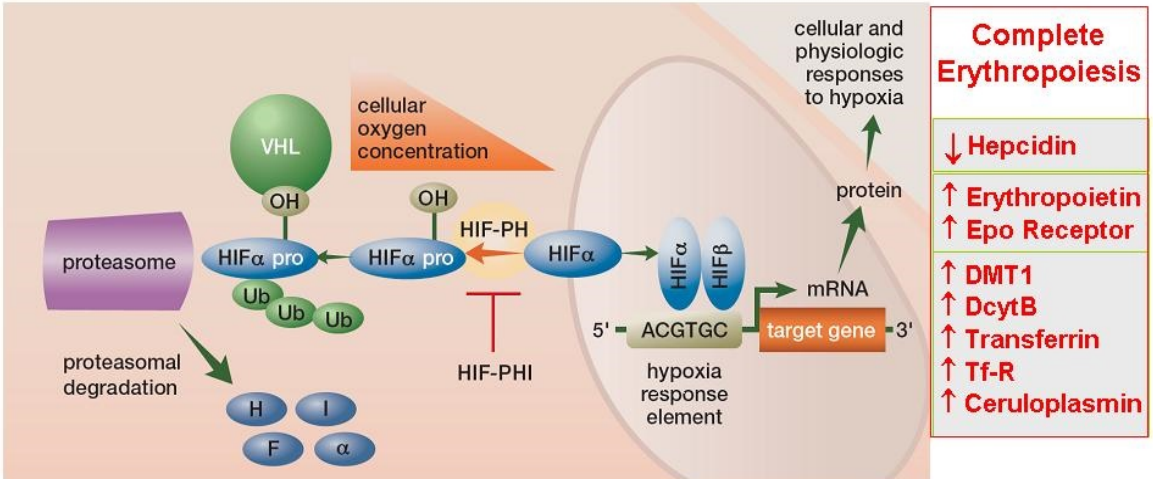
Roxadustat is an oral medication that could potentially deliver effective treatment of CKD-related anemia with less need for iron supplementation and without producing supraphysiologic levels of circulating EPO, which may translate into an improved safety profile.

2.4 Mechanism of Action of Roxadustat

Virtually all tissues depend on a sufficient supply of oxygen for survival. Lack of oxygen associated with hypoxic, ischemic, and anemic conditions triggers a series of homeostatic responses (Figure 1). Hypoxia-inducible factor (HIF) is a transcription factor that is believed to be the key element in the body's oxygen sensing mechanism (Semenza, 2000). HIF regulates expression of genes that modulate both the acute and chronic response to hypoxia, and HIF-responsive genes regulate processes as diverse as erythropoiesis, iron metabolism, oxidation, cellular metabolism, glycolysis, vasculogenesis, cell cycle progression, and apoptosis. Chronic

hypoxia and intermittent hypoxia induce different sets of genes associated with HIF transcriptional activity (Fan, 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, with each heterodimeric isoform responsible for the induction of specific sets of genes (Greijer, 2005; Hu, 2003). For example, HIF-1α has been shown to regulate vascular endothelial growth factor (VEGF) expression (Gray, 2005; Buchler, 2003), while HIF-2α is critical for the induction of the EPO gene and erythropoiesis (Warnecke, 2004; Scortegagna, 2005).

Figure 1. HIF-PHI Mechanism of Action



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

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

HIF target genes are expressed when the active heterodimer binds to a conserved deoxyribonucleic acid (DNA) motif found within all HIF target genes, termed the hypoxia response element, and in cooperation with other coactivators 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, their accumulation under normoxic conditions is prevented by recruitment and binding by the von Hippel-Lindau (VHL) protein, which targets HIF-α isoforms for degradation through the ubiquitin-proteasome pathway. The molecular mechanism for oxygen-dependent degradation of HIF-α is based on the hydroxylation of specific proline residues, as catalyzed by a family of HIF prolyl hydroxylases (HIF-PH) that utilize molecular oxygen as the substrate for hydroxylation. Thus, HIF-PH constitutes the body's main oxygen sensor by regulating the prevalence and activity of nuclear HIF protein. Under hypoxic conditions, HIF-PHs are inactive and lead to initiation of the HIF-responsive transcriptional cascade (Wang, 1995; Semenza, 1998).

Roxadustat is a potent and reversible HIF-PH inhibitor (HIF-PHI) that transiently induces HIF stabilization and leads to a functional HIF transcriptional response that mimics the erythropoietic

response associated with exposure of humans to intermittent hypoxia. HIF induces expression of not only EPO, but also the EPO receptor and proteins that promote iron absorption and recycling 9 (Peyssonnau, 2008). Thus, roxadustat pharmacologically stimulates erythropoiesis via the HIF pathway and in a manner consistent with the body's normal homeostatic response to anemia, but under normoxic conditions. In contrast to the classical paradigm, suggesting that anemia in CKD patients is caused by the inability of these patients to produce EPO, results of a study of roxadustat treatment of CKD subjects not requiring dialysis (Study No. FGCL-SM4592-017) suggest that the kidneys and other sites of EPO production in this patient population retain the ability to produce sufficient EPO for robust erythropoiesis.

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

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

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

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

2.5 Clinical Experience with Roxadustat

Roxadustat is currently being studied in dialysis and nondialysis CKD subjects with anemia. Numerous Phase 1 and 2 clinical studies have been completed, in the United States, Europe, and Asia. Information from these studies is provided below and in the most recent Investigator's Brochure.

As of 14 September 2014, an estimated total of 1,485 subjects have been exposed to roxadustat in the clinical development program, comprising 571 healthy subjects and an estimated 483 subjects with nondialysis-dependent chronic kidney disease (NDD-CKD) and 431 subjects with dialysis-dependent chronic kidney disease (DD-CKD). In completed studies, subjects with CKD have received up to 24 weeks of roxadustat, in doses of up to 3.0 mg/kg. In completed Phase 1 studies, healthy volunteers received single doses of roxadustat up to 4.0 mg/kg and repeat doses up to 3.75 mg/kg three times weekly (TIW) for 4 weeks. In a completed thorough QT study in healthy volunteers, single doses up to 5 mg/kg were administered, without evidence of QT prolongation.

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

2.5.1 Pharmacokinetics and Pharmacodynamics

The pharmacokinetics (PK) and pharmacodynamics (PD) of roxadustat were characterized in studies in healthy volunteers and in dialysis and nondialysis CKD subjects. Roxadustat showed generally dose proportional PK (except at the lowest dose of 0.3 mg/kg); $t_{1/2}$ was 12 to 14 hours in healthy volunteers, and 15 to 19 hours in dialysis subjects (after a single 1 and 2 mg/kg dose).

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

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

In PD 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 predialysis and postdialysis. 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, 2009). In a clinical study with dialysis subjects, the reported mean administered individual ESA dose was 8,000 IU, which would correspond to plasma EPO C_{max} levels exceeding 3,000 mIU/mL (Fishbane, 2007). This is approximately 10-fold higher than the physiologic range.

2.5.2 Efficacy

Data from a 4-week treatment study in anemic CKD subjects not on dialysis (Study FGCL-SM4592-017) showed that roxadustat promotes erythropoiesis at lower doses in CKD subjects than in healthy volunteers. With roxadustat 0.7 mg/kg TIW dosing, mean Hb increased by 1.0 g/dL over a 6-week period in anemic CKD subjects who completed 4 weeks of dosing; more robust mean Hb increases of 2.0 to 2.3 g/dL occurred at roxadustat doses of 1.5 and 2.0 mg/kg TIW, respectively. Hemoglobin responder (Hb increase of ≥ 1.0 g/dL) rates were 62%, 60%, 91%, and 100% in the roxadustat 0.7, 1.0, 1.5, and 2.0 mg/kg TIW cohorts, respectively. With the additional criterion that Hb achieve a level of ≥ 11 g/dL as well as increasing by ≥ 1.0 g/dL, the Hb responder rate with roxadustat 2.0 mg/kg was 91% with TIW dosing. The rapid rates of rise in Hb with roxadustat treatment were not accompanied by elevations in blood pressure, as has been reported with ESA treatment (Eschbach, 1989).

Data from a 16- to 24-week treatment study in CKD subjects not on dialysis (Study FGCL-4592-041) showed that absolute and weight-based doses of roxadustat, administered TIW and BIW, effectively corrected and maintained Hb levels to a target of 11 g/dL (range of 11 -13 g/dL in 96 subjects and 10.5 -12.0 g/dL in 48 subjects). The median time to Hb response was 28 days for subjects who received adequate weight-based or absolute starting doses of roxadustat and longer for those who received a lower absolute starting dose. Dose-response trends suggested that starting doses of 1.0−1.6 mg/kg roxadustat administered TIW are appropriate to correct Hb levels during 4 weeks of treatment in nondialysis CKD subjects. Once Hb correction is achieved, a dose frequency reduction appears to be feasible to maintain Hb levels.

Data from a 6- and 19-week treatment study in ESRD subjects on dialysis (Study FGCL-4592-040) showed the feasibility of converting subjects from a stable ESA dose to roxadustat. In the 6-week dose range portion of this conversion study (during which roxadustat doses were mostly fixed upon switching from stable doses of epoetin alfa), a dose response was observed. The 1.0 mg/kg roxadustat dose was comparable to the epoetin alfa control, which had a small decline in Hb levels from baseline and a lower percent Hb responder rate compared with 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. In the 19-week portion of the study, during which dose-titration was allowed, Hb maintenance was demonstrated to be durable in roxadustat treatment arms (combined) over a 19-week period. 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.

2.5.3 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 comorbidities and on a number of concomitant medications. Safety analyses did not reveal any association between the rates of occurrence of cardiovascular

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

In general, the most commonly reported adverse events (AEs; ≥ 4% and ≥ 1% above placebo rate) in healthy subjects were headache and dizziness. The most commonly reported AEs (≥ 5%) in subjects with NDD-CKD were diarrhea, nausea, urinary tract infection, nasopharyngitis, peripheral edema, hyperkalemia, headache, and hypertension (none were ≥ 8%). The most commonly reported AEs (≥ 3%) in subjects with DD-CKD were diarrhea, nausea, hypertension, and upper respiratory tract infection (none were ≥ 5%). Adverse event rates of hypertension (1% in Study FGCL-SM4592-017, and 7.6% in Study FGCL-4592-041) and thrombosis (overall incidence < 1%) compare favorably with the rates reported in published ESA studies in similar patient populations (Krapf, 2009; Fishbane, 2007). No safety risks could be associated with rate of rise of Hb levels or with achieving any Hb level above 11 g/dL using roxadustat. FGCL-4592-041 study subjects achieved Hb ≥ 11 g/dL in > 50% of the exposure time during study, and there were no cardiovascular safety events (death, MI, stroke, unstable angina, hospitalization for congestive heart failure, or hospitalization for arrhythmias) 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 seen infrequently, 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. For detailed safety information, please refer to the most current version of the Investigator's Brochure (IB).

2.6 Summary

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

2.7 Roxadustat Dose Rationale

Starting doses of roxadustat were studied in three ways in the Phase 2 clinical development program: 1) using an absolute weight-based dosing approach that was useful in the proof of concept stage; 2) using a tiered weight-based approach where a subject's starting dose was selected based on categorizing the subject's body weight as low (45 to 60 kg), medium (> 60 to 90 kg), or high (> 90 to 140 kg); and 3) 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.

The tiered, weight-based roxadustat starting doses selected for this study are 70 mg for subjects who weigh <70 kg and 100 mg for subjects who weigh ≥ 70 kg. These dose tiers are based primarily on the safety and efficacy data generated in the CKD non-dialysis correction of anemia

study (FGCL-4592-041), adjusted slightly downward at equivalent weights to achieve slower Hb correction and lower levels in the present study. These starting doses will be administered at a dosing frequency of TIW. Using this dosing scheme, subjects will receive starting roxadustat doses ranging between 0.6 to 1.6 mg/kg TIW across the eligible weight range for the present study. This is comparable to the starting doses that effectively corrected Hb levels in study FGCL-4592-041. Further dose adjustment to achieve correction and subsequent maintenance is based upon regular monitoring of Hb and application of a dose adjustment algorithm, which was successfully used in Phase 2, with minor modification for ease of use in Phase 3.

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. Prespecified dosing steps were used to correct and maintain Hb based on absolute Hb levels and change in 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 maintenance and will be adopted in this study with minor modifications.

2.8 Risks/Benefits of Roxadustat Treatment

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

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

The safety of treatment with roxadustat and placebo will be carefully monitored. Adverse and serious adverse events, and laboratory parameters including CBC, electrolytes, liver enzymes, CPK, and iron indices, will be closely monitored. An independent expert panel will assess and adjudicate prespecified cardiovascular, cerebrovascular, and thromboembolic events. In addition, an independent Data and Safety Monitoring Board (DSMB) will perform regular, periodic assessments of safety data to detect any potential safety signals that may arise during the study and advise the Sponsor accordingly.

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

3 OBJECTIVES

3.1 Primary Objectives

The primary objectives of this study are to:

- Evaluate the efficacy of roxadustat for the treatment of anemia (correction and maintenance of Hb) in CKD subjects not on dialysis.
- Evaluate the safety of roxadustat administered over a minimum of 52 weeks of treatment.

3.2 Secondary Objectives

The secondary objectives in this study are to:

- Evaluate the effect of roxadustat in CKD anemia on:
    - Serum lipid parameters
    - HRQoL
    - Blood pressure
    - The need for anemia rescue therapy: red blood cell (RBC) transfusion, or ESA, or intravenous (IV) iron
    - Time to achieve Hb response

4 STUDY DESIGN

4.1 Description of the Study

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of roxadustat in the treatment of anemic subjects with Stage 3, 4 or 5 CKD who are not on dialysis. This study is planned to recruit up to 1200 subjects from approximately 200 study centers worldwide.

This study will consist of three study periods as follows:

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

  (*or enroll into an Open Label Extension study)

Refer to Appendix 3 for a diagrammatic representation of the study schema.

Following the Screening Period, subjects will be randomized in a 2:1 ratio to receive roxadustat (approximately 800 subjects) or placebo (approximately 400 subjects). Dosing will be TIW throughout the study, except in subjects who have already converted to BIW or QW dosing regimens as a result of being enrolled under previous Study FGCL-4592-060 protocol versions. Starting doses of , respectively.

Table 1. Treatment Arms

Treatment Arms	Correction	Maintenance	n (FG-4592)	n (Placebo)
1A	TIW	QW	100[a]	0
1P	TIW	QW	0	50[a]
2A	TIW	BIW	100	0
2P	TIW	BIW	0	50
3A	TIW	TIW	100	0
3P	TIW	TIW	0	50

Abbreviations: A = active control; BIW = twice a week; n = number of subjects; P = placebo; TIW = three times a week; QW = once a week.

[a] These numbers are based on a sample size of 450 and will increase if the overall sample size increases.

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

Table 2. Initial Study Drug (FG-4592 or Placebo) Dosing

Study Drug (Dose Frequency)	**Low Weight** (<70 kg)	**Medium Weight** (70 to 100 kg)	**High Weight** (>100 kg)
FG-4592/Placebo (TIW)	70 mg	100 mg	120 mg

Abbreviations: TIW = three times a week; QW = once a week.

Study drug will be dose adjusted according to anemia correction guidelines until subjects achieve a Hb value of ≥ 11 g/dL and ≥ 1 g/dL increase from baseline by central lab. Once these criteria are met, subjects will enter into the maintenance phase of anemia treatment and will be dose-adjusted according to maintenance guidelines (Section 4.5.2, Appendix 1).

Study drug dose will remain constant during the first 4 weeks of the Treatment Period, unless a dose reduction is required for excessive hematopoiesis. Dose adjustments are permitted starting at Week 4, and at intervals of every 4 weeks thereafter.

4.2 Randomization and Treatment Assignment

Up to 1200 planned subjects will be randomized to receive either roxadustat or placebo in a double-blind manner, resulting in approximately 800 subjects receiving roxadustat and approximately 400 subjects receiving placebo.

Randomization is stratified by the following factors:

- Screening Hb values (≤ 8 g/dL vs > 8 g/dL)
- History of cardiovascular, cerebrovascular or thromboembolic diseases (Yes vs No)
- eGFR (< 30 mL/min/1.73 m^2 vs ≥ 30 mL/min/1.73 m^2)
- Geographic region (US vs Ex-US).

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

4.3 Replacement of Subjects

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

4.4 Blinding

This is a double-blind, placebo-controlled study. The Investigator, study site staff, subject, and the Sponsor and designees, are blinded to study drug assignment, but not to the dose. Additionally, all efforts should be made to keep subjects blinded to study Hb values.

4.4.1 Maintenance of Blinding

Neither the subjects nor the Investigators and their staff can distinguish the roxadustat tablets from the matching placebo tablets. Both will be identical in appearance, packaging, and labeling in order to maintain the blind.

4.4.2 Planned and Unplanned Unblinding of Treatment Assignment

Treatment assignments will be unblinded after the completion of the study.

Any intentional or unintentional breaking of the blind should be reported and documented. Breaking the blind (for a single subject) should be considered only when knowledge of the treatment assignment is deemed essential by the Investigator for the subject's care. Unplanned unblinding will result in the discontinuation of subject participation from the study. When possible and appropriate the blind will be maintained for Sponsor personnel responsible for analysis and interpretation of results at the study's conclusion.

4.5 Study Treatment

4.5.1 Dose and Schedule Overview

Subjects will be randomized via IWRS to receive roxadustat or placebo. Dosing will be TIW throughout the study, except in subjects who have already converted to BIW or QW dosing regimens under previous Study FGCL-4592-060 protocol versions.

The initial study drug dose (per dose amount) is based on the tiered, weight-based dosing scheme (Table 3) and the first study drug administration will be on Day 1 (Week 0).

Table 3. Initial Study Drug (FG-4592 or Placebo) Dosing

Tiered Weight Category	<70 kg	≥70 kg
Initial Tiered Weight Dose (TIW)	70 mg	100 mg

Abbreviations: TIW = three times weekly.

Study drug dose will remain constant during the first 4 weeks of the Treatment Period, unless a dose reduction is required for excessive hematopoiesis. Dose adjustments are permitted starting at Week 4, and at intervals of every 4 weeks thereafter. Starting doses of study drug will be dose-adjusted according to anemia correction guidelines until subjects achieve a Hb value of ≥ 11 g/dL and ≥ 1 g/dL increase from baseline by central lab. Once these criteria are met, subjects will enter into the maintenance phase of anemia treatment and will be dose-adjusted according to maintenance guidelines (Section 4.5.2 and Appendix 1). Study drug doses will be considered as meeting the definition of TIW if they are administered at least 2 days apart, and no more than 4 days apart. Subjects enrolled under previous FGCL-060-4592 protocols will continue taking study drug BIW or QW if they have already converted to those dosing frequencies. Study drug doses taken BIW must be administered at least 3 days apart, and no more than 5 days apart. Study drug doses taken QW must be administered at least 5 days apart, and no more than 9 days apart.

During the Treatment Period, subjects will attend consecutive weekly study visits for the first 2 weeks of study treatment (from Weeks 0 to 2) followed by every other week study visits starting at Week 4 until week 24. After Week 24, subjects will attend study visits every 4 weeks until the end of the Treatment Period. Treatment duration is variable for individual subjects. In order to complete the Treatment Period simultaneously for all study subjects, the minimum treatment duration may be less than 52 weeks, with a maximum treatment duration of up to 3 years after the last subject is randomized. After the Treatment Period, study subjects may enter a separate Open Label Extension study or will proceed to the 4-week post-treatment Follow-up Period, and will attend a final study visit at 4 weeks after end of treatment.

4.5.2 Dose Adjustment

Dose adjustments will occur in two separate study-dosing phases. All subjects will start with the Correction Phase during which an attempt to correct their Hb levels is made (Section 4.5.2.1). If successfully corrected, the subject will then enter into the Maintenance Phase. Each of these phases will follow unique dose adjustment rules per Appendix 1.The determination of Hb response and transition from the Correction to Maintenance Phase of the study is based on central laboratory Hb values.

4.5.2.1 Correction Phase of Dosing

The aim of the Correction Phase is to increase Hb levels from baseline to a level that avoids the need for blood transfusion, by using the dose adjustment algorithm in Appendix 1, and taking into account physiologic fluctuations and test variability. This phase is variable in length for each subject, depending on when the subject achieves a Hb level ≥11.0 g/dL and ≥1.0 g/dL increase from baseline by central lab.

Study drug dose will remain constant during the first 4 weeks of the Treatment Period, unless a dose reduction is required for excessive hematopoiesis (Appendix 1).

All dose adjustments are based on Hb values using HemoCue, a point-of-care device. 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 to be resumed at 4-week intervals. For example, if the subject's Hb increases > 2.0g/dL from Weeks 2 to 3, the subject's dose is reduced by one dose step at Week 3. The next dose adjustment review occurs 4 weeks later at Week 7 and at 4-week intervals thereafter.

If the dose adjustment interval falls on a nonvisit study week the dose adjustment review should be performed at the next scheduled clinic visit. For example, if a subject's visit is scheduled for Weeks 10 and 12, and the dose adjustment should occur at Week 11, then the dose adjustment should be evaluated at the Week 12 visit.

4.5.2.2 Maintenance Phase of Dosing

The aim of the Maintenance Phase is to maintain Hb levels after the initial correction by utilizing the dose adjustment algorithm described in Appendix 1 and taking into account physiologic fluctuations and test variability.

Dose adjustment reviews will continue every 4 weeks. If the dose adjustment interval falls on a nonvisit study week, the dose adjustment review should be performed at the next scheduled clinic visit. For example, if a subject's visit is scheduled for Weeks 10 and 12, but the dose adjustment review falls on Week 11, then the dose adjustment should be evaluated at the Week 12 visit and at 4-week intervals thereafter.

- Given the complexities of the dose adjustment algorithm, and the need to take into consideration various clinical parameters, it is not considered a protocol deviation when study subjects are dosed based on their clinical circumstance, whether or not this is concordant with the roxadustat dosing algorithm, **unless** it is related to "excessive hematopoiesis" (refer to Section 4.5.1) or "Overdose" (prescribed >3.0 mg/kg per dose)

4.6 Concomitant Medications, Procedures and Nondrug Therapies

4.6.1 Concomitant Medications

Concomitant medications are any prescription or over-the-counter preparations, including herbal products and "natural remedies", used by a subject while participating in this clinical study, including those taken within 30 days prior to screening.

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

To avoid confounding effects on study endpoints, changes to antihypertensive medications should be minimized, and made only if deemed medically necessary by the Investigator or if prespecified changes in blood pressure are met. A similar consideration should be made for lipid lowering therapies.

4.6.1.1 Statin interaction

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

Table 4. Recommended Maximum Daily Dose of Statins for Subjects in FGCL-4592-060

Statin	Recommended maximum dose (mg/day)
Atorvastatin	40
Simvastatin	20 (5 if eGFR < 30 mL/min)
Rosuvastatin	10
Pravastatin	40
Fluvastatin	40 (20 if eGFR < 30 mL/min)
Pitavastatin	2 (1 if eGFR < 30 mL/min)
Lovastatin	20

Abbreviations: eGFR = estimated glomerular filtration rate.

4.6.1.2 Phosphate Binders

When coadministered with phosphate binders in a clinical pharmacology study, the bioavailability of roxadustat was reduced. Subjects should be advised to discuss with the investigator when changing the dose or dosing time of their phosphate binder, including high dose calcium used for this purpose. To optimize absorption of roxadustat, it is recommended that subjects take roxadustat at least 1 hour before or 3 hours after their phosphate binder, if possible.

4.6.1.3 Supplemental Iron Use

Oral iron is recommended for dietary supplementation to support erythropoiesis and as the first-line for prevention and treatment of iron deficiency, unless the patient is intolerant to this route of treatment. The recommended daily oral dose for the treatment of iron deficiency is 200 mg of elemental iron. Intravenous iron is restricted as rescue therapy, using the Rescue Therapy Guidelines below.

4.6.2 Rescue Therapy Guidelines

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

4.6.2.1 Red Blood Cell Transfusion

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

4.6.2.2 Erythropoiesis-Stimulating Agent (ESA)

Use of *more than two* courses of ESA for anemia rescue is a withdrawal criterion requiring early termination from study treatment. Nevertheless, criteria are provided in order to standardize the use of ESA rescue. The Investigator should consider initiating use of an approved ESA only if all of the following criteria are met:

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

ESA treatment must be stopped after 4 weeks of use or when Hb ≥ 9 g/dL is reached, whichever occurs first. Study drug treatment may be resumed after the following intervals:

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

After two successful courses of rescue with ESA and return to study drug, subjects who again meet the above criteria for ESA rescue and receive a third course of ESA must be discontinued from the study drug at this point. Such a subject will complete procedures for early termination and subsequent modified follow-up according to the procedures outlined in Section 7.1.2.6, if consent is not withdrawn to do so.

Note: ESA administration in during hospitalization: Such ESA use is not considered a protocol deviation, if study subjects have no access to study drug while hospitalized.

4.6.2.3 Intravenous Iron

The use of intravenous iron is discouraged in the setting of this placebo-controlled trial. In roxadustat phase 2 studies where IV iron was restricted, iron repletion was not required for

treatment of anemia. IV iron is not standard of care in CKD nondialysis patients in most regions of the world. Therefore, the subject may receive IV iron supplementation only if each of the following criteria are met:

- The subject has not responded adequately to two or more dose increases or the maximum dose (by body weight) of study drug; **and**
- The subject is unresponsive to or does not tolerate oral iron; **and**
- Ferritin levels are < 100 ng/mL (< 220 pmol/L) **or** transferrin saturation is (TSAT) < 20%

If IV iron rescue criteria are met, the dose in a single administration (day) should be no more than 250 mg. The selection and dosing of the IV iron formulation should be consistent with regional package inserts that are applicable to CKD-ND patients. Study drug treatment may continue during IV iron administration.

At 4 to 8 weeks after the single dose of IV iron, a repeat dose of IV iron can be administered if the Hb remains < 9 g/dL AND the subject still meets iron deficiency criteria (ferritin < 100 ng/mL(< 220 pmol/L) or TSAT < 20%). After this 8 week period, full IV iron rescue criteria would need to be met again in order to qualify a subject for a second course of IV iron at a later point in the trial.

4.6.3 Therapeutic Phlebotomy

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

4.6.4 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.

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

- Androgens and iron-chelating agents (eg, deferoxamine, deferiprone, or deferasirox therapy)
- Dapsone
- Acetaminophen or paracetamol > 2.0 g/day or > 500 mg per dose repeated every 6 hours if use is chronic or consistent
- Use of herbal medicine is not prohibited but strongly discouraged
    - RBC transfusion or IV iron administration that does not meet the rescue criteria described in Section 4.6.2.1

- ESA administration that does not meet the rescue criteria described in Section 4.6.2.2. Additionally, if a subject meets rescue criteria and receives more than two courses of ESA for anemia rescue, such a subject should be discontinued from the study drug.

  Note: ESA administration in during hospitalization: Such ESA use is not considered a protocol deviation, if study subjects have no access to study drug while hospitalized.

4.6.5 Contraception

Female subjects of childbearing potential must agree to practice a dual method of contraception, for example, a combination of the following: (1) oral contraceptive, depot progesterone, or intrauterine device; and (2) a barrier method (condom or diaphragm). Male subjects with female partners of childbearing potential who are not using birth control as described above must use a barrier method of contraception (eg, condom) if not surgically sterile (ie, vasectomy). Contraceptive methods must be practiced upon entering the study and through 12 weeks after the last dose of study treatment. If a subject discontinues prematurely, the contraceptive method must be practiced for 12 weeks following final administration of study drug. Sexual abstinence satisfies the contraceptive requirement.

Pregnancy, spontaneous or therapeutic abortion, or events related to pregnancy must be reported (see Section 10.3.6).

4.7 Safety Monitoring Plan

Safety will be assessed throughout the study. A complete baseline profile of each subject will be established through demographics, medical history, clinical laboratory values, vital signs, physical assessments, and electrocardiogram (ECGs). During the course of the study, vital signs, complete and targeted physical assessments, laboratory tests, and ECGs will be performed at regular intervals. Any medically significant changes from baseline will be monitored throughout the study and appropriate interventions will be taken accordingly. Clinical laboratory tests may be assessed at additional times on unscheduled visits for safety reasons. Liver function abnormalities will be managed according to the liver safety and monitoring guidance (Appendix 4).

Adverse events, SAEs, and ongoing concomitant medication usage will be monitored and recorded throughout the study. Serious adverse event reports will be evaluated individually to assess for the impact of the event, if any, on the overall safety of the product and on the study itself. Cumulative AEs will be monitored throughout the study. Serious adverse events and AEs will be followed until resolved, stable, or until the subject's End of Study (EOS) Visit. See Section 10.2.1 for details on AE and SAE reporting.

Prespecified and adjudicated cardiovascular, cerebrovascular, and thromboembolic safety events of interest (ie, death, MI, stroke, congestive heart failure requiring hospitalization, and unstable angina requiring hospitalization), hypertensive emergency, deep vein thrombosis [DVT], pulmonary embolism [PE], and vascular access thrombosis [VAT]) will be captured. A separate adjudication charter will describe the process in detail, and training and training materials will be provided to study sites. The CV adjudication committee will review blinded events in this study and in other studies of roxadustat across the development program for anemia of CKD.

4.8 Data Safety and Monitoring Board

A Data Safety Monitoring Board (DSMB) will review prespecified safety data periodically in collaboration with the Sponsor to ensure subject safety. The DSMB will review data in this study

and in other studies of roxadustat across the development program for anemia of CKD. A separate charter will establish the rules, meeting frequency and scope of responsibilities of the DSMB.

5 STUDY ENROLLMENT AND DISCONTINUATION

5.1 Inclusion Criteria

1. Age ≥ 18 years
2. Subject has been informed of the investigational nature of this study and has given written informed consent in accordance with institutional, local, and national guidelines
3. Diagnosis of CKD, with Kidney Disease Outcomes Quality Initiative (KDOQI) Stage 3, 4, or 5, not receiving dialysis; with an eGFR < 60 mL/min/1.73 m^2 estimated using the abbreviated 4-variable Modification of Diet in Renal Disease (MDRD) equation
4. Mean of the three most recent Hb values during the Screening Period, obtained at least 4 days apart, must be ≤ 10.0 g/dL, with a difference of ≤ 1.0 g/dL between the highest and the lowest values. The last screening Hb value must be within 10 days prior to randomization
5. Ferritin ≥ 30 ng/mL(≥ 66 pmol/L)
6. TSAT ≥ 5%
7. Serum folate level ≥ lower limit of normal (LLN)
8. Serum vitamin B_{12} level ≥ LLN
9. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 x upper limit of normal (ULN), and total bilirubin (Tbili) ≤ 1.5 x ULN
10. Body weight 45 to 160 kg

5.2 Exclusion Criteria

1. Any ESA treatment within 12 weeks prior to randomization
2. More than one dose of IV iron within 12 weeks prior to randomization
3. RBC transfusion within 8 weeks prior to randomization
4. Active, clinically significant infection that could be manifested by white blood cell (WBC) count > ULN, and/or fever, in conjunction with clinical signs or symptoms of infection
5. History of chronic liver disease (eg, chronic infectious hepatitis, chronic auto-immune liver disease, cirrhosis, or fibrosis of the liver)
6. New York Heart Association Class III or IV congestive heart failure
7. Myocardial infarction, acute coronary syndrome, stroke, seizure, or a thromboembolic event (eg, deep vein thrombosis or pulmonary embolism) within 12 weeks prior to randomization
8. Systolic BP ≥ 160 mmHg or diastolic BP ≥ 95 mmHg (confirmed by repeat measurement), within 2 weeks prior to randomization
9. Diagnosis or suspicion (eg, complex kidney cyst of Bosniak Category 2F or higher) of renal cell carcinoma on renal ultrasound within 12 weeks prior to randomization

10. History of malignancy, exceptions made for the following malignancies: a) those determined to be cured or in remission for ≥ 5 years, b) curatively resected basal cell or squamous cell skin cancers, c) cervical cancer in situ, or resected colonic polyps
11. Positive for any of the following: human immunodeficiency virus (HIV); hepatitis B surface antigen (HBsAg); or antihepatitis C virus antibody (anti-HCV Ab)
12. Chronic inflammatory disease that could impact erythropoiesis or is determined to be the principal cause of anemia (eg, systemic lupus erythematosus, rheumatoid arthritis, celiac disease) even if it is currently in remission
13. Known untreated proliferative diabetic retinopathy, diabetic macular edema, macular degeneration and retinal vein occlusion
14. Known history of myelodysplastic syndrome or multiple myeloma
15. Known hereditary hematologic disease such as clinically apparent thalassemia or sickle cell anemia, pure red cell aplasia, or other known causes for anemia other than CKD
16. Known hemosiderosis, hemochromatosis, coagulation disorder, or hypercoagulable condition
17. Any prior organ transplant (that has not been explanted), or a scheduled organ transplantation
18. Anticipated elective surgery that is expected to lead to significant blood loss or anticipated elective coronary revascularization
19. Known active or chronic gastrointestinal bleeding
20. Any prior treatment with roxadustat or a hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI)
21. Use of iron-chelating agents within 4 weeks prior to randomization
22. Use of an investigational drug or treatment, participation in an investigational study, or presence of expected carryover effect of an investigational treatment, within 4 weeks prior to randomization
23. Anticipated use of dapsone or androgens in any dose amount or anticipated chronic use of acetaminophen or paracetamol > 2.0 g/day during the treatment or follow-up periods of the study
24. History of alcohol or drug abuse within 2 years prior to randomization
25. Females of childbearing potential, unless using contraception as detailed in the protocol, or sexual abstinence; male subjects with sexual partners of childbearing potential who are not on birth control unless the male subject agrees to use contraception, or sexual abstinence
26. Pregnant or breastfeeding females
27. Any medical condition that in the opinion of the Investigator or Sponsor may pose a safety risk to a subject in this study, which may confound efficacy or safety assessment, or may interfere with study participation

5.3 Subject Discontinuation

Subjects may discontinue from the study at any time. Discontinued subjects should be encouraged to complete the ET and the EOS visit procedures. The reason for subject discontinuation will be documented. Subjects will then continue to be followed up for vital status, safety events requiring potential adjudication, as well as important concomitant medication use (eg, ESA), at periodic intervals of 3-6 months until the end of the overall study, unless the subject withdraws consent for this modified follow-up.

Subjects should be discontinued from the study for any of the following reasons:

- Subject no longer consents to participate in the study
- Investigator's decision that it is in the best interest of the subject to be withdrawn from the study
- Significant noncompliance with study procedures, as determined by Investigator or Sponsor
- Subject is lost to follow-up
- Pregnancy
- Death
- Subjects who receive more than 2 courses of ESA rescue that meets the protocol-specified rescue criteria

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

6 INVESTIGATIONAL PRODUCT

6.1 Formulation

Roxadustat and placebo drug product are supplied by FibroGen, Inc. as red coated, oval tablets for oral administration, in strengths of 20 mg, 50 mg and 100 mg. The excipients include lactose monohydrate, microcrystalline cellulose, povidone, croscarmellose sodium, magnesium stearate, and colorant Red Opadry II. All ingredients used for manufacture of roxadustat and placebo tablets comply with US and European Union compendial or regulatory standards. Strengths are different in size, and debossing reflects the strength (ie, 20, 50 or 100 mg). Placebo tablets match the roxadustat tablets in appearance and size. Both active and placebo tablets are presented in white High-density polyethylene (HDPE) bottles with a black lining, for optimal light protection, and closed with a foil induction seal and a white, child resistant cap. Due to the light-sensitive nature of roxadustat and to minimize exposure of the active pharmaceutical ingredient to light, tablets should remain in the original packaging for as long as possible and be administered as intact tablets only.

6.2 Storage

Roxadustat and placebo tablets should be protected from light, and stored at 15º to 30ºC (59º to 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.

6.3 Study Drug Handling and Disposal

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

6.4 Administration

Study drug dispensing to subjects will generally occur every two weeks for the first 24 weeks and then every four weeks for the remainder of the study, with instructions for self-administration of the tablets on each dosing day, according to the dosing schedule. The first dose may be administered at the study site after completion of procedures or may be taken at home. The tablets are to be swallowed whole with water. Dosing should occur at approximately the same time of day. The subject may take the study drug with or without food.

Study drug doses will be considered as meeting the definition of TIW if they are administered at least 2 days apart, and no more than 4 days apart. Subjects enrolled under previous FGCL-4592-060 protocols will continue taking study drug BIW or QW if they have already converted to those dosing frequencies. Study drug doses taken BIW must be administered at least 3 days apart, and no more than 5 days apart. Study drug doses taken QW must be administered at least 5 days apart, and no more than 9 days apart. It may facilitate dosing if the days of the week of dosing remain consistent throughout the study, but this is not mandatory.

Compliance with study drug dosing will be closely monitored and recorded throughout the study to enable a determination of whether a subject meets sufficient overall compliance with study therapy, which will be defined in the Statistical Analysis Plan (SAP). For study drug handling and disposal please refer to the Study Manual.

See Section 2.1 and Appendix 1 for dose adjustments.

7 STUDY PROCEDURES

7.1 Study Procedures by Visit

7.1.1 Screening Period (Up to 6 Weeks)

Subjects must be consented before any screening tests or assessments are performed. For all screen failures, the reason(s) will be documented.

7.1.1.1 Screening 1

- Signed written informed consent
- Inclusion/Exclusion criteria verification
- Demographics and medical history
- Complete physical examination
- Height, weight
- Blood pressure, heart rate
- Laboratory tests:
    - Complete blood count (CBC) with WBC differential
    - Serum chemistry
    - Lipid panel (fasting whenever possible)
    - Serum iron, ferritin, TIBC, TSAT
    - Reticulocyte Hb Content (CHr)
    - Hemoglobin A1c (HbA1c)
    - Vitamin B_{12} and folate
    - Enzyme-linked immunosorbent assay (ELISA) for HIV
    - Hepatitis B surface antigen and anti-HCV Ab
    - Urine human chorionic gonadotropin (hCG) pregnancy test for women of childbearing potential only
- Adverse event recording
- Concomitant medication recording
- Procedures and nondrug therapy recording

7.1.1.2 Screening 2

Hemoglobin values must be obtained at least 4 days apart.

- Blood pressure, heart rate
- Hemoglobin only
- Renal ultrasound to exclude renal carcinoma- not required if results of a previous renal ultrasound within 3 months prior to randomization are available. If no results are

available, a renal ultrasound must be performed during screening, *at or after* the Screening 2 visit.

- Adverse event recording
- Concomitant medication recording
- Procedures and nondrug therapy recording

7.1.1.3 Screening 3

Hemoglobin values must be obtained at least 4 days apart.

- Blood pressure, heart rate
- Hemoglobin only
- Adverse event recording
- Concomitant medication recording
- Procedures and nondrug therapy recording

7.1.1.4 Additional Screening

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

For example, an additional Hb value may be collected if necessary. The mean of the 3 most recent Hb values during the screening period, obtained at least 4 days apart, will be used to calculate the subject's eligibility. Iron, Vitamin B12, and folate may be repeated once during the screening period if necessary, in particular if these have been supplemented during the screening period. Other labs pertaining to the eligibility criteria should not be repeated unless there is reason to believe the initial value(s) is/are incorrect, and not without the prior approval of the Sponsor's medical monitor. If subjects fail screening, they may be rescreened as deemed appropriate, with approval by the Sponsor's medical monitor.

7.1.2 Treatment Period

Eligible subjects will be randomized via IWRS to receive roxadustat or placebo. The Treatment Period begins on the first day of dosing with study treatment (Day 1/Week 0). Scheduled visit days will be calculated from first day of dosing (Day 1/Week 0), for example: Week 1 (Day 8 ±2 days), Week 12 (Day 85 ±2 days), Week 48 (Day 336 ±3 days), etc.

7.1.2.1 Day 1 (Week 0)

All assessments are to be completed prior to study drug administration.

- Inclusion/Exclusion criteria verification
- Complete physical examination
- Weight
- Blood pressure, heart rate, respiratory rate, temperature
- Laboratory tests
    - Urinalysis, including microalbumin/creatinine ratio
    - CBC with WBC differential

  - Serum chemistry
  - Lipid panel (fasting, whenever possible)
  - Serum iron, ferritin, TIBC, TSAT
  - CHr
  - HbA1c
  - Reticulocyte count
  - Special laboratory analytes: Hepcidin and high sensitivity-C-reactive protein (hs-CRP)
  - Archival serum/plasma samples(optional donation, separate consent form)
- HemoCue assessment
  - Point of care qualitative urine pregnancy test for women of child bearing potential only
- HRQoL questionnaires (SF-36, FACT-An, and European Quality Of Life Questionnaire in Five Dimensions, Five Levels [EQ-5D-5L])
- 12-lead electrocardiogram
- Adverse event recording
- Concomitant medication recording
- Procedures and nondrug therapy recording
- Dispense study drug (2 weeks supply)

7.1.2.2 Weeks 1 and 2 (Weekly, ±2 days)

- Laboratory tests (must be performed prior to next dosing week):
  - CBC with WBC differential
  - Week 2 only: Liver Function Test (LFTs) and CPK
  - Week 2 only: CHr
  - Reticulocyte count
- HemoCue assessment
- Dose adjustment review in the event of excessive hematopoiesis. Refer to Section 2.1 and Appendix 1.
- BP and heart rate
- Adverse event recording

- Concomitant medication recording
- Procedures and nondrug therapy recording
- Dispense study drug, 2 weeks supply (Week 2 only)

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

- Laboratory tests (must be performed prior to next dosing cycle):
    - Weeks 4, 8, 12, and 20: CBC with WBC differential
    - Week 6 followed by every visit where no CBC is collected: Hb only
    - Weeks 4, 8, 12, and 20: Serum chemistry
    - Weeks 6 and 16: LFTs and CPK only
    - Weeks 4, 8, 12, and 20: Lipid panel (fasting whenever possible)
    - Weeks 4, 8, 12, and 20: Serum iron, ferritin, TIBC, TSAT
    - Weeks 4, 6, 8, 12, and 20: CHr
    - Week 12 only: HbA1c
    - Weeks 8, 12, and 20: Reticulocyte count
    - Weeks 4, 12, and 20: Special laboratory analytes (hepcidin, hsCRP)
    - Weeks 4, 12, and 20: Archival serum/plasma samples (optional donation, separate consent form)
- HemoCue assessment
- Weeks 12 and 24: Targeted physical examination
    - Weeks 12 and 24: Point of care qualitative urine pregnancy test for women of child bearing potential only
- Dose adjustment review beginning at Week 4 followed by every 4 weeks thereafter (except/or more frequently in the event of excessive hematopoiesis). Refer to Section 2.1 and Appendix 1.
- Week 12 only: HRQoL questionnaires (SF-36, FACT-An, and EQ-5D-5L)
- Adverse event recording
- Concomitant medication recording
- Procedures and nondrug therapy recording

- Dispense study drug
    - Weeks 4 to 22 (2 week supply)
        - Week 24 (4 week supply)

7.1.2.4 Week 28 to End of Treatment (Every 4 weeks, ± 3 days)

- Laboratory tests (must be performed prior to next dosing cycle):
    - Week 28 followed by every 8 weeks: CBC with WBC differential
    - Week 28 followed by every visit where no CBC is collected: Hb only
    - Week 28 followed by every 8 weeks: Serum chemistry
    - Weeks 28, 36, 44, and 52 followed by every 12 weeks: Lipid panel (fasting whenever possible)
    - Week 28 followed by every 8 weeks: Serum iron, ferritin, TIBC, TSAT
    - Week 28 followed by every 8 weeks: CHr
    - Week 28 followed by every 16 weeks: HbA1c
    - Weeks 44, 68 and 84: Reticulocyte count
    - Weeks 44, 68 and 84: Special laboratory analytes (hepcidin, hsCRP)
    - Weeks 44, 68 and 84: Archival serum/plasma samples (optional donation, separate consent form)
- HemoCue assessment
- Week 36 followed by every 12 weeks: Targeted physical examination
    - Week 36 followed by every 12 weeks: Point of care qualitative urine pregnancy test for women of child bearing potential only
- Weeks 28, 52, and 76: 12-lead electrocardiogram
    - Dose adjustment review every 4 weeks (except/or more frequently in the event of excessive hematopoiesis). Refer to Section 2.1 and Appendix 1.
- All visit weeks: BP and B.
- All visit weeks: BP and heart rate
- Weeks 28, 52, and 76: HRQoL questionnaires (SF-36, FACT-An, and EQ-5D-5L)
- Adverse event recording
- Concomitant medication recording

- Procedures and nondrug therapy recording
- Dispense study drug (4 weeks supply), except at End of Treatment

7.1.2.5 End of Treatment (EOT) (± 3 days)

- Laboratory tests:
    - CBC with WBC differential
    - Serum chemistry
    - Lipid panel (fasting whenever possible)
    - Serum iron, ferritin, TIBC, TSAT
    - CHr
    - HbA1c
    - Reticulocyte count
    - Special laboratory analytes (hepcidin, hs-CRP)
    - Archival serum/plasma samples (optional donation, separate consent form)
- Complete physical examination
- Blood pressure, heart rate, respiration rate, temperature
    - Point of care qualitative urine pregnancy test for women of childbearing potential only
- HRQoL questionnaires (SF-36, FACT-An, and EQ-5D-5L)
- 12-lead electrocardiogram
- Adverse event recording
- Concomitant medication recording
- Procedures and nondrug therapy recording

7.1.2.6 Early Termination (ET)

If a subject discontinues from the study during the Treatment Period prior to completing treatment, the Investigator should perform the End of Treatment/Early Termination (EOT/ET) assessments as soon as possible after withdrawal from dosing (Section 5.3). Whenever possible, the subject should also return for a follow-up visit to complete the End of Study (EOS) assessments (Section 7.1.3.1). Such a subject will be considered a noncompleter of the treatment and/or the study, regardless of whether the patient conducts the EOT assessments at early termination and/or the early EOS visit(s). These subjects will continue to be followed for vital status, safety events requiring potential adjudication, as well as important concomitant medication use (eg, ESA), at periodic intervals of 3 to 6 months until the end of the overall study, or unless the subject withdraws consent for this modified follow-up.

7.1.3 Post-Treatment Follow-Up Period

7.1.3.1 End of Study (EOS): 4 weeks after EOT (or ET) (± 2 days)

- Laboratory tests:
  - CBC with WBC differential
  - Serum chemistry
  - Lipid panel (fasting whenever possible)
  - Serum iron, ferritin, TIBC, TSAT
  - CHr
  - HbA1c
  - Reticulocyte count
  - Special laboratory analytes (hepcidin, hs-CRP)
  - Archival serum/plasma samples (optional donation, separate consent form)
- Targeted physical examination
- Blood pressure, heart rate
- Point of care qualitative urine pregnancy test for women of childbearing potential only
- Adverse event recording
- Concomitant medication recording
- Procedures and nondrug therapy recording

7.2 Missed Visits

Every attempt should be made to complete all study visits as outlined in the Schedule of Assessments (Appendix 2).

If a subject fails to return for scheduled visits, a documented effort must be made to return the patient to the study or to determine the reason for failed return. If the subject cannot be reached by telephone, a certified/registered letter should be sent to the subject (or the subject's legally authorized representative, if appropriate) requesting contact with the Investigator. This information should be recorded in the study records.

7.3 Unscheduled Visits

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

7.4 Laboratory Assessments

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

7.4.1 HemoCue

Hemoglobin values obtained by HemoCue are used to allow "real-time" dose adjustments for all subjects. HemoCue results will be collected in the CRF.

7.4.2 Central Laboratory

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

Unscheduled and repeat laboratory tests will also be performed by the central laboratory. However, if the turnaround time from the central laboratory is not sufficiently rapid for clinical management of the subject, local laboratory test results may be used to make the necessary clinical judgments.

A Central Laboratory Manual with instructions on specimen collection, processing, storing, and shipping to the central laboratory will be provided to all participating sites.

Laboratory parameters to be measured in this study are as described in Table 5.

Table 5. Laboratory Tests

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

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

7.4.3 Archival Serum/Plasma Samples

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

7.5 Electrocardiogram

Local 12-lead ECGs will be performed on all subjects at baseline Day 1 (Week 0) prior to first treatment and treatment Weeks 28, 52, and 76, and at EOT (or ET).

7.6 Renal Ultrasound

A renal ultrasound examination will be required within 3 months prior to randomization. If not on record within this timeframe, the subject should have a renal ultrasound performed during screening, at or after Screening Visit 2. Renal ultrasound must exclude the presence or suspicion of renal cell carcinoma for patient to be eligible. Sites are reminded to schedule the renal ultrasound in a timely manner.

7.7 Health-Related Quality of Life Questionnaires

All study subjects will be required to complete HRQoL questionnaires (SF-36, FACT-An, and EQ-5D-5L) at Day 1 (Week 0), treatment Weeks 8, 12, 28, 52, and 76, and at EOT (or ET). Health-related quality of life assessments should be administered approximately at the same time of day.

7.7.1 36-Item Short Form Health Survey

The 36-Item Short Form Health Survey (SF-36) is a QoL instrument designed to assess generic health concepts relevant across age, disease, and treatment groups. It is aimed at both adults and adolescents ages eighteen years and older. The SF-36 consists of eight domains of health status: physical functioning (PF) (10 items), role physical (4 items), bodily pain (2 items), general health (5 items), vitality (4 items), social functioning (2 items), role emotional (3 items) and mental health (5 items). Two component scores, the Physical Component Scores and the Mental Component Summary can also be calculated. For both the SF-36 domain scores and summary scores, higher scores indicate better health status.

7.7.2 FACT-An

The Functional Assessment of Cancer Therapy—General (FACT-G; Version 4) contains 27 items that cover four dimensions of well-being: physical (7 items), functional (7 items), social/family (7 items), and emotional (6 items). A subscale of 13 fatigue specific items plus 7 additional items related to anemia were developed for use in conjunction with the FACT-G (Cella 1997). The 13 fatigue items plus the 7 additional items related to anemia comprise the Anemia Subscale. Administration of the FACT-G plus the Anemia Subscale is referred to as the FACT-An. The FACT-An has a recall period of the ‘past seven days’. Respondents are asked to provide responses, (ie, ‘Not at all’, ‘A little bit’, ‘Somewhat’, ‘Quite a bit’ and ‘Very much’), to a list of statements which are either positively or negatively phrased. For all FACT-An scales, a higher score indicates better QoL.

7.7.3 European Quality of Life Questionnaire in Five Dimensions, Five Levels (EQ-5D-5L)

The EQ-5D-5L consists of the EQ-5D-5L descriptive system and the EQ-5D-5L visual analog scale. The EQ-5D-5L descriptive system comprises five dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, extreme problems. The visual analog scale records the respondent's self-rated health status on a graduated (0 to 100) scale, where the endpoints are labeled ‘Best imaginable health state’ and ‘Worst imaginable health state’ with higher scores for higher HRQoL. The EQ-5D-5L health states, defined by the EQ-5D-5L descriptive system, may be converted into a single summary index by applying a formula that essentially attaches values (also called weights) to each of the levels in each dimension.

7.8 Blood Pressure Measurement

Blood pressure and heart rate should be performed with the subject comfortably at rest for a minimum of 5 minutes, in the seated position with the legs uncrossed, and the back and arm supported, such that the middle of the cuff on the upper arm is at the level of the right atrium (the midpoint of the sternum). If another position is required, that position should be utilized consistently throughout the study. The subject will be instructed to relax as much as possible and to refrain from talking during the measurement procedure. Preferably, measurement will be done with an electronic automated oscillometric device. From Day 1 through EOT/ET, blood pressure must be taken and recorded in triplicate, at least 5 minutes apart.

8 ENDPOINTS AND ASSESSMENTS

8.1 Primary Efficacy Endpoint

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

The **primary endpoint for the US (FDA)** submission is defined as the change in Hb from baseline to the average level during the evaluation period (defined as Week 28 until Week 52).

The **primary endpoint for the Ex-US** submission is defined as the proportion of subjects who achieve a Hb response at two consecutive visits during the first 24 weeks of treatment, without rescue therapy (ie, RBC transfusion, ESA, or IV iron)

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

- Hemoglobin ≥ 11 g/dL and Hb increase from baseline by ≥ 1 g/dL in subjects with baseline Hb > 8 g/dL, or
- An increase in Hb by ≥ 2 g/dL in subjects with baseline Hb ≤ 8.0 g/dL

8.2 Secondary Endpoints

The secondary efficacy endpoints in this study are:

- For Ex-US submission only: Hb maintenance: Mean change from baseline (CFB) in Hb averaged over 8 weeks of treatment at Weeks 28 to 36, without rescue therapy within 6 weeks prior to and during this 8-week evaluation period.
- Mean CFB in LDL cholesterol averaged over Weeks 12 to 28
- Mean CFB in the SF-36 PF subscore averaged over Weeks 12 to 28 in the Intent to Treat (ITT) subjects with baseline PF subscore below 35
- Mean CFB in SF-36 Vitality subscore averaged over Weeks 12 to 28 in ITT subjects with baseline vitality subscore below 50
- Blood pressure effect
    a. Mean CFB in mean arterial pressure (MAP) averaged over Weeks 20 to 28, measured as the mean of the triplicate measurements 5 minutes apart
    b. Time to (and proportion of subjects with) worsened hypertension (defined as systolic BP > 170 mmHg or diastolic BP > 110 mmHg measured, and an increase from baseline of ≥ 20 mmHg [systolic BP] or ≥ 15 mmHg [diastolic BP], confirmed by the mean of triplicate measurements 5 minutes apart)
- Time to (and proportion of subjects who received) rescue therapy (composite of RBC transfusion, ESA use, and IV iron) in the first 24 weeks of treatment
- Time to (and proportion of subjects who received) rescue therapy (composite of RBC transfusion, ESA use, and IV iron) in the first 52 weeks of treatment

8.3 Additional Evaluation of Efficacy

Hemoglobin correction and maintenance:

- For Ex-US submission only: Mean Hb level averaged over 8 weeks of treatment at Weeks 28 to 36, without rescue therapy within 6 weeks prior to and during this 8-week evaluation period
- For Ex-US submission only: Time to first Hb response as defined by the primary endpoint for Ex-US submission
- Change from baseline in Hb at each of the selected postdosing time points

Hospitalization

- Percentage (%) of subjects hospitalized
- Number of days of hospitalization per patient-year exposure (PEY)

Rescue therapy use

- Time to (and proportion of subjects who receive) RBC transfusions
- Number of RBC packs per patient-month exposure to study medication
- Number of ESA-week dose per PEY: 1~3 doses of epoetin alfa or beta or biosimilar thereof (in Europe) administered within 1 week = 1 ESA-week; 1 darbepoetin subcutaneous (subcut) or IV dose = 2 ESA-week; 1 Mircera IV or subcut dose = 4 ESA-week; 1 peginesatide dose IV or subcut = 4 ESA-week

Changes in cholesterol levels

- Change from baseline at each of the selected treatment time points in:
    - Total cholesterol
    - Low-density lipoprotein/high-density lipoprotein ratio
    - Non-HDL cholesterol
- Proportion of subjects achieving LDL target of < 100 mg/dL averaged over Weeks 12 to 28 of treatment

Blood pressure effect

- Proportion of subjects achieving blood pressure treatment goal in CKD subjects (systolic BP < 130 mmHg systolic and diastolic BP < 80 mmHg) based upon the average blood pressures over Weeks 12 to 28 of treatment

Health-Related Quality of Life (HRQoL) and European Quality of Life in Five Dimensions, Five Levels (EQ-5D-5L) benefits of anemia therapy in subjects with CKD anemia

- Mean CFB averaged over Weeks 12 to 28 of treatment in:
    - Vitality Subscale of SF-36
        - In all ITT subjects
    - Physical Functioning (PF) Subscale of SF-36
        - In all ITT subjects

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

Hepcidin, Iron Parameters, HbA1c, and CKD Progression

- Change from baseline in serum hepcidin at each of the selected treatment time points
- Change from baseline in serum ferritin at each of the selected treatment time points, subgrouped by baseline values of < 100 ng/mL, 100to 400 ng/mL, and > 400 ng/mL
- Change from baseline in TSAT at each of the selected postdosing time points, subgrouped by baseline values of < 20%, 20% to 40%, and > 40%
- Change from baseline in HbA1c level at each of the selected treatment time points in all subjects, in subjects with history of diabetes and those with no diabetes
- Rate of progression of CKD: rate of change in eGFR over time adjusted by baseline eGFR
- Proportion of subjects requiring renal replacement therapy, adjusted by baseline eGFR

8.4 Safety Assessments and Endpoints

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

- AEs, SAEs, and clinically significant changes in laboratory values from baseline
- Vital signs, ECG parameters, and clinical laboratory values

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

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

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

- *For US (FDA) Only: The primary safety endpoint in this study is the MACE (Major Adverse Cardiac Event) composite endpoint, defined as time to first occurrence of death from all causes, MI, or stroke, only for the purpose of being pooled across multiple similar studies in the Phase 3 program. None of the individual studies are powered to meet the MACE primary safety endpoint individually. The pooled MACE analysis is only for purposes of supporting a US FDA regulatory filing of roxadustat.*
- The above adjudicated safety events may also be used to support the pooled analyses of additional composite safety endpoints across multiple studies in the Phase 3 program, such as MACE+ (death, MI, stroke, congestive heart failure requiring hospitalization, and unstable angina requiring hospitalization), or a composite which consists of all of the adjudicated events.

9 STATISTICAL CONSIDERATIONS

9.1 Sample Size Determination

A total of up to 1200 planned subjects will be randomized in a 2:1 ratio to receive either roxadustat (approximately 800 subjects) or placebo (approximately 400 subjects) in a double-blind manner.

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

For US (FDA) Submission Primary Efficacy Endpoint

A sample size of 450 will have > 99% power to detect a 1 g/dL difference in mean Hb values between the two treatment groups, assuming that the common standard deviation is 1.2 g/dL, using an analysis of variance (ANOVA) test with a 0.05 two-sided significance level.

For the comparisons of individual treatment arms versus pooled placebo, a sample size of 35 roxadustat and 150 placebo will have 90% power to detect a 0.75 g/dL difference in mean Hb values between the two treatment groups, assuming that the common standard deviation is 1.2 g/dL, using an ANOVA test with a 0.05 two-sided significance level.

For Ex-US Submission Primary Efficacy Endpoint

Based on a two-sided test at the alpha = 0.05 level of significance, the study will have > 95% power to demonstrate a statistically significant difference between roxadustat and placebo, assuming that the proportion of subjects with a Hb response in the roxadustat group is at least 65% and the cumulative proportion of subjects with a Hb response in the placebo group is at most 25%.

During the course of this Phase 3 study, which is being conducted in parallel with other Phase 3 studies, up to 1200 subjects may be enrolled in this study to support the overall safety evaluation of roxadustat across pooled multiple studies in the Phase 3 program, including adjudicated composite safety endpoints of interest. The study will stop enrollment at the Sponsor's discretion if: 1) the minimum of 450 subjects has been achieved to support the primary endpoint in this individual study, and 2) sufficient safety events of interest have been accumulated across the nondialysis Phase 3 program to support a pooled analysis of these events across multiple studies in the same population.

9.2 Analysis Populations

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

- **Intent-to-Treat Population (ITT):** All randomized/enrolled subjects. All efficacy data will be analyzed using the ITT population.
- **Safety Population:** All subjects who took any dose of study medication will be included in the safety population. All safety data will be analyzed using the safety population.
- **Per Protocol Set (PPS):** All randomized/enrolled subjects who receive at least 12 weeks of study treatment, have valid corresponding Hb measurements, and are without major

protocol violations. The PPS population will be utilized for supportive analysis of primary and secondary endpoints. Full criteria for PPS exclusion will be specified in the SAP.

9.3 Interim Analysis

The study will have no interim analysis with statistical inference. Safety data and dosing decisions will be monitored on an ongoing basis. Additional ongoing review of safety data will be conducted by an independent DSMB (see Section 4.8).

9.4 Statistical Analysis

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

9.4.1 Subject Enrollment, Accountability and Disposition

A table will provide the number of enrolled subjects, Safety, ITT and PPS subjects, subjects who are completers of the treatment period, subjects who are completers of the study (treatment and follow-up), and subjects who terminated the Treatment Period early along with the reason for early termination.

9.4.2 Demographics and Baseline Characteristics

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

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

9.4.3 Efficacy Analyses

Hemoglobin results obtained from the central laboratory will be used for all efficacy analyses. Baseline Hb is defined as the mean of the last four central laboratory Hb values prior to the first dose of study treatment. Hemoglobin values after a rescue therapy will not be excluded for the US (FDA) submission primary efficacy analysis. Hemoglobin values within 6 weeks after a rescue therapy will be excluded for the Ex-US submission primary efficacy endpoint as well as other sensitivity efficacy analyses. For subjects with missing values, the MMRM model will be used for missing data handling unless otherwise specified.

9.4.3.1 Primary Efficacy Analysis

The primary efficacy endpoint will be analyzed using the ITT population as the primary analysis population and PPS population as a supportive analysis population.

For US (FDA) Submission

The primary efficacy endpoint for the US (FDA) submission is the Hb CFB to the average level during the evaluation period, defined as Weeks 28 to 52.

The planned treatment duration is at least 52 weeks. The rationale for choosing the specified evaluation period as the primary endpoint for US (FDA) submission is that one would expect to have achieved Hb correction by Week 28, and averaging it to Week 52 would be an accurate reflection of a longer term therapeutic effect of roxadustat.

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

H_0: Hb CFB to the average of Weeks 28 to 52 in the roxadustat group = Hb CFB to the average of Weeks 28 to 52 in the placebo group

Versus

H_1: Hb CFB to the average of Weeks 28 to 52 in the roxadustat group = Hb CFB to the average of Weeks 28 to 52 in the placebo group

A Multiple Imputation Analysis of Covariance model (MI ANCOVA) will be used to compare the roxadustat and pooled placebo groups in a fixed sequence procedure: 1) pooled roxadustat (TIW+BIW+QW) vs. pooled placebo, 2) roxadustat TIW vs. pooled placebo, 3) roxadustat BIW vs. pooled placebo, 4) roxadustat QW vs. pooled placebo. The latter are being performed to test the BIW and QW maintenance dosing frequencies that are enrolled from earlier versions of the protocol. If a null hypothesis is rejected, the claim of the tested roxadustat regimen over placebo will be declared successful and the test will progress to the next comparison in sequence.

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

Hemoglobin values under the influence of a rescue therapy will not be censored in the primary analysis. The model will contain terms for treatment arm, baseline measurement, visit, visit by treatment arm, and other randomization stratification factors. The primary efficacy analysis will be based on the estimated difference in the overall mean effect between the two treatment groups throughout the evaluation period based on the MI ANCOVA model.

For Ex-US Submission

The primary efficacy endpoint for the Ex-US submission of proportion of responders will be compared using Cochran-Mantel-Haenszel (CMH) adjusting for the stratification factors comparing the pooled roxadustat (TIW+BIW+QW) to pooled placebo (TIW+BIW+QW). The hypothesis to be tested for the primary efficacy analysis is:

H_0: Hb responder rate in the roxadustat group = Hb responder rate in Placebo group

Versus

H_1: Hb responder rate in the roxadustat group ≠ Hb responder rate in Placebo

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

The 95% CIs based on CMH adjusted odds ratio will be reported. In addition, the 95% CIs of the responder rate based on the exact method of Clopper-Pearson will be calculated and presented.

The impact of missing data on the analysis of the primary efficacy endpoint will be examined using sensitivity analyses detailed in a SAP.

9.4.3.2 Secondary Efficacy Analyses

The secondary efficacy endpoints will be analyzed using the ITT population as the primary analysis population and PPS population as a supportive analysis population.

A Mixed Model of Repeated Measures will be used to compare the roxadustat and pooled placebo groups in a fixed sequence procedure. Secondary endpoints will be tested using a fixed sequence approach to adjust for multiple endpoints comparing between the pooled roxadustat vs. pooled placebo, followed by roxadustat TIW vs. pooled placebo. If a null hypothesis is rejected, the claim of roxadustat over placebo will be declared successful and the test will progress to the next comparison in sequence.

1. Ex-US only: Mean CFB in Hb averaged over 8 weeks of treatment at Weeks 28 to 36, without rescue therapy within 6 weeks prior to and during this 8-week evaluation period for the 2 treatment groups (in a fixed sequence of pooled roxadustat vs. pooled placebo, followed by roxadustat TIW vs pooled placebo) will be compared using an MMRM model with baseline Hb and eGFR as covariates and treatment group, visit, treatment*visit, and the other randomization stratification factors as fixed effects. The test for this endpoint will compare the roxadustat group to pooled placebo. Separately, as an exploratory analysis to assess the effect of the QW and BIW maintenance dosing frequencies, pairwise comparisons of roxadustat BIW and QW (from the original and amendment 1 versions of the protocol) to pooled placebo (1P+2P+3P) will also be performed.
2. Mean CFB in LDL cholesterol averaged over Weeks 12 to 28 for the 2 treatment groups (pooled roxadustat vs pooled placebo) will be compared using MMRM models with baseline value as covariate and stratification factors as fixed effects.
3. Mean CFB in the SF-36 PF subscore averaged over Weeks 12 to 28 in the ITT subjects with baseline PF subscore below 35 for the 2 treatment groups will be compared using an MMRM model as outlined above .
4. Mean CFB in the SF-36 Vitality subscore averaged over Weeks 12 to 28 in the ITT subjects with baseline vitality subscore below 50 for the two treatment groups will be compared using an MMRM model as outlined above.
5. Mean CFB in MAP averaged over Weeks 20 to 28 for the two treatment groups will be compared using an MMRM model as outlined above.
6. Time to (and proportion of subjects with) protocol defined worsened hypertension for the pooled roxadustat vs pooled placebo will be compared using Cox Proportional Hazards model adjusting for stratification factors. A hazard ratio and its associated 95% CI will be computed between the roxadustat group versus pooled placebo. Noninferiority will be declared if the upper bound of the 2-sided 95% CIs of the odds ratio does not exceed 1.3. Superiority will be declared if the upper bound of the 2-sided 95% CI of the odds ratio does not exceed one. The incidence rate per PEY by treatment group will also be reported.
7. Time to (and proportion of subjects who received) rescue therapy (composite of RBC transfusion, ESA use, and IV iron) over the first 24 and first 52 weeks for the roxadustat TIW group versus pooled placebo will be compared using Cox Proportional Hazards model adjusting for stratification factors. A hazard ratio and its associated 95% CI will be computed between the roxadustat group versus pooled placebo. Superiority will be

declared if the upper bound of the 2-sided 95% CI of the hazard ratio does not exceed one.

Comparisons of the individual treatment arms from the original and Amendment 1 versions of the protocol (ie, BIW, QW) in roxadustat against pooled placebo will be reported descriptively. Subgroup analyses will also be performed for primary and secondary endpoints by sex, age group, etc.

Due to the large amount of visits to include in the model, the unstructured covariance pattern model will be applied first. If the algorithm for unstructured covariance pattern does not converge, then the heterogeneous Toeplitz structure will be used instead. If this second model also does not converge, then the (homogeneous) Toeplitz structure will be tried, and finally compound symmetry as a covariance structure to achieve convergence.

9.4.3.3 Additional Efficacy Analyses

The additional efficacy analyses will use the ITT population.

Additional efficacy analyses of continuous endpoints will use an MMRM model using baseline value as covariate and other stratification factors as fixed effects.

Additional analyses of proportions will use the CMH model adjusting for stratification factors. A CMH adjusted odds ratio and its associated 95% CI will be computed to compare between the roxadustat TIW group and pooled placebo. A two-sided 95% CI of the proportion based on the exact method of Clopper-Pearson will be computed for each treatment group.

Additional efficacy analyses of time-to-event endpoints will use the Cox Proportional Hazards model adjusting for stratification factors. Median time to event and associated 95% CI will be estimated using Kaplan-Meier method.

9.4.4 Safety Analyses

Safety analyses will be performed using the Safety Population. Safety parameters include adverse events, laboratory parameters, vital signs, and ECG parameters. For each safety parameter, unless otherwise specified, the last assessment made prior to the first dose of double-blind study medication will be used as the baseline for all analyses. The analytical methods for the composite safety endpoints of interest will be described in a region-specific pooled SAP to reflect the nature of the pooling of these endpoints across multiple studies in the Phase 3 program and the region-specific safety endpoints.

9.4.4.1 Adverse Events

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

An AE (classified by preferred term) occurring during the double-blind treatment period will be considered a treatment emergent adverse event (TEAE) if it was not present prior to the first dose of study medication, or it was present prior to the first dose of study medication but increased in severity during the double-blind treatment period. An AE that occurs more than 28 days after the last dose of study medication will not be counted as a TEAE.

The number and percentage of subjects reporting TEAEs in each treatment group will be tabulated by system organ class (SOC) and preferred term; by SOC, preferred term, and severity; and by SOC, preferred term, and relationship. If more than one event occurs with the same preferred term for the same subject, the subject will be counted only once for that preferred term

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

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

The number and percentage of subjects reporting common (≥ 5% of subjects in any treatment group) TEAEs, Treatment-Emergent serious AEs (TESAE), fatal SAEs (ie, events that caused death), and AEs leading to discontinuation of study medication will be summarized by SOC, preferred term and treatment group, sorted in decreasing frequency overall

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

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

9.4.4.2 Clinical Laboratory Parameters

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

9.4.4.3 Vital Signs

Descriptive statistics for vital signs (eg, systolic and diastolic blood pressure, and pulse rate) and their changes from baseline at each visit, and for the maximum and minimum value on treatment will be presented by treatment group.

9.4.4.4 Electrocardiogram

Descriptive statistics for ECG parameters (eg, Heart Rate, PR interval, QRS interval, QT interval, and QTc interval) at baseline and changes from baseline at each assessment time point and for the maximum and minimum value on treatment will be presented by treatment group. QTc interval will be calculated using both Bazett (QTcB = QT/(RR)1/2) and Fridericia (QTcF = QT/(RR)1/3) corrections; and if RR is not available, it will be replaced with 60/heart rate (HR) in the correction formula. To assess potentially clinically meaningful ECG abnormalities, the number and percentage of subjects with postbaseline ECG values outside a predefined range or limit of change will be tabulated by treatment group, as well as shift tables for results of ECG interpretation (normal, abnormal not significant, abnormal significant).

9.5 Statistical Analysis Plan

A detailed SAP will be finalized prior to the final database lock. Any significant changes to the analyses described in this protocol will be highlighted in the SAP and the Clinical Study Report. The analytical methods for the composite safety endpoints of interest will be described in a region-specific pooled SAP to reflect the nature of the pooling of these endpoints across comparable studies in the Phase 3 program and the region-specific safety endpoints.

9.5.1 Protocol Deviation

Due to the complex study design and standard of clinical practice, the following issues should not be captured and reported as protocol deviations.

- Given the complexities of the dose adjustment algorithm, and the need to take into consideration various clinical parameters, it is not considered a protocol deviation when study subjects are dosed based on their clinical circumstance, whether or not this is concordant with the roxadustat dosing algorithm, **unless** it is related to "excessive hematopoiesis" (refer to Section 4.5.1) or "Overdose" (prescribed >3.0 mg/kg per dose).
- ESA administration in during hospitalization: Such ESA use is not considered a protocol deviation, if study subjects have no access to study drug while hospitalized.

10 SAFETY

10.1 Background

Adverse event reports from Investigators are the critical building blocks to the developing safety profile of the study drug. Subjects will be asked nonleading questions in general terms to determine the occurrence of AEs, according to the schedule outlined in Appendix 2. In addition, all AEs reported spontaneously during the course of the study will be recorded. The Investigator must immediately (within 24 hours of awareness) report to the sponsor all SAEs, regardless of whether the Investigator believes they are related to the study drug.

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

10.2 Definitions

10.2.1 Definition of an Adverse Event

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

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

An AE includes medical conditions, signs, and symptoms not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with an underlying condition that were not present prior to the AE reporting period (see Section 10.3.1).

10.2.2 Definition of a Serious Adverse Event

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

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

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

10.2.3 Definition of a Suspected Adverse Reaction

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

10.2.4 Definition of an Adverse Reaction

An adverse reaction means any adverse event caused by a drug.

10.3 Procedures for Eliciting, Recording, and Reporting Adverse Events

10.3.1 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 dose of study drug, except for pregnancy reporting (see Section 10.3.6). In addition, all AEs reported spontaneously by the subject to site personnel, outside the study period, may be recorded.

AEs will be followed until resolved, stable, or until the subject's last study visit or lost to follow-up. If an AE is not resolved or stabilized at the subject's last visit, it is up to the discretion of the Investigator and Sponsor's Medical Monitor to determine if further monitoring of the event is warranted.

AEs collected prior to dosing of study drug will be considered "nontreatment emergent" while those reported after the first dose of study drug and up to 28 days after the last dose of study drug will be considered "treatment emergent" and be assessed for relationship to study drug.

10.3.2 Adverse Event Eliciting/Reporting

During the AE reporting period, study site personnel will query each subject at each visit to actively solicit any AE occurring since the previous visit. All AEs will be collected in response to a general question about the subject's well-being and any possible changes from the baseline or previous visit, but shall not be specifically solicited. There will be no directed questioning for any specific AE. This does not preclude the site from collecting and recording any AEs reported by the subject to site personnel at any other time.

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

The following attributes must be assigned to each adverse event:

- Description (Investigator's verbatim term describing the event)
- Dates of onset and resolution

- Severity
- Judgment of relationship to blinded study drug
- Outcome
- Action taken regarding study drug as a direct result of the adverse event
- Other treatment required
- Determination of "seriousness"

10.3.3 Assessing Adverse Event Severity

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

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

10.3.4 Assessing the Adverse Event's Relationship to Study Drug

Most of the information about the safety of a drug prior to marketing comes from clinical studies; 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 being possibly related or related to study drug.

Related (Adverse Reaction):

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

Possibly Related (Suspected Adverse Reaction):

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

Not Related:

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

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, Sponsor is responsible for making the final causality assessment for individual reports, and for reporting suspected adverse reactions and adverse reactions to Health Authorities.

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

10.3.5 Reporting Serious Adverse Events on the SAE Report Form

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

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

Full details of the SAE should also be recorded on the medical records and in the CRF. All correspondence on SAEs must be marked URGENT. The following minimum information is required:

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

Follow-up information for the event should be sent promptly (within 7 days) as necessary.

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

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

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

10.3.5.2 Deaths

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

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

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

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

10.3.6 Pregnancies: Reporting and Follow-up of Subjects

A pregnancy in a female subject or a male subject's female partner must be confirmed by a positive serum β-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 12 weeks after the last dose of study treatment, a Pregnancy Report Form must be completed and submitted to Sponsor (by way of its designated safety management vendor) within 24 hours of the Investigator learning of the pregnancy. If applicable, a pregnant subject is immediately withdrawn from receiving study treatment. The Investigator must follow the pregnancy to completion to ascertain both its outcome and whether any AEs occur.

Pregnancy itself is not an AE. However, the Investigator should report the information to the Sponsor on the designated forms. Pregnancies are followed up to outcome. The outcome period may vary in length from birth to one year of age, depending on the initial outcome and circumstance of the birth. The initial outcome of the pregnancy/birth must be reported by the Investigator on a Pregnancy Outcome Report Form, which should be sent to the Sponsor and/or its designated safety management vendor within 24 hours of the Investigator learning of the

outcome. Follow-up pregnancy outcome reports may be required for longer follow-up of the newborn.

10.3.7 Definition and Reporting of Overdose

The maximum tolerated dose of roxadustat has not been established in humans. For the purpose of this study, the maximum allowed roxadustat dose is 300 mg/dose or 3.0 mg/kg/dose, whichever is lower. Any dose exceeding this should be reported within 24 hours, except in patients who may be on maximum doses of 400 mg/dose or 3.5 mg/kg/dose from previous versions of the protocol. Those patients will undergo a dose adjustment to the new maximum dose level in the present protocol, at the next scheduled visit. The Sponsor's Medical Monitor should also be informed of an overdose as soon as possible. In an event of a suspected roxadustat overdose, the subject should be monitored closely. Symptoms associated with an overdose, if any, will be reported as an adverse event. An overdose without associated symptoms is not an AE and will be recorded on the overdose CRF only.

10.3.8 Abnormal Laboratory Findings

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

An abnormal laboratory finding in absence of any other signs or symptoms is not necessarily an AE/SAE. If the abnormal laboratory finding meets criteria for an AE/SAE, report the underlying diagnosis in lieu of the abnormal laboratory value.

Clinically significant laboratory abnormalities that reflect a change from the initial screening value and that require active management are to be considered by the Investigator as AEs (eg, abnormalities that require study treatment dose modification, discontinuation, more frequent follow-up assessments).

11 DIRECT ACCESS TO SOURCE DOCUMENTS

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

The purpose of study monitoring is to verify the following:

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

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

12 QUALITY CONTROL AND QUALITY ASSURANCE

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 site visit
- Routine study site monitoring
- Documented study and system training
- CRF and query review against source documents

12.2 Audit and Inspection

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

13 ETHICS

13.1 Ethical Considerations

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

13.2 Communication with the Institutional Review Board or Independent Ethics Committee

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

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

Investigators are also responsible for promptly informing the IRB/IEC of any protocol changes or amendments, changes to the Investigator's Brochure, and other safety-related communications from Sponsor. 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 Informed Consent Form (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 Sponsor for regulatory purposes.

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

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 Health Insurance Portability

and Accountability Act (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 DATA HANDLING AND RECORD KEEPING

14.1 Source Documents

Source records are original documents, data, and records that are relevant to the clinical study. The Investigator will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each subject enrolled in this clinical study. Source records must be adequate to reconstruct all data transcribed onto the CRFs and resolved queries.

14.2 Data Collection, Handling, and Verification

All required data will be entered onto CRFs/eCRFs by authorized site personnel. or will be provided as a data transfer from authorized service providers (such as laboratory results from a central laboratory). Data will be entered or uploaded into a validated, clinical database compliant with 21 CFR Part 11 regulations. The database will be a secured, password-protected system with full audit trail.

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

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

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

15 INVESTIGATOR REQUIREMENTS

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

15.1 Study Drug Accountability

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

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

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

15.2 Disclosure of Data

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

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

15.3 Retention of Records

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

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

16 FINANCING AND INSURANCE

Financing and insurance are addressed in a separate document.

17 PUBLICATION POLICY

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

18 REFERENCES

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19 APPENDICES

Appendix 1 Dose Adjustment Algorithm

		CORRECTION PHASE		MAINTENANCE PHASE			
Change in Hb From 4 Wks Prior (g/dL)	**(To achieve initial Hb response)**	**Hb ≥ 13.0g/dL**	**Maintenance**	**Hb < 10.5 g/dL**	**Hb 10.5 to 11.9 g/dL**	**Hb 12.0 to 12.9 g/dL**	**Hb ≥ 13.0 g/dL**
< -1.0	↑	Hold, then resume dosing using maintenance phase rules when: Hb ≤ 11.9 g/dL, at a dose that is reduced by two dose steps		↑	↑	No change	Hold, then resume dosing when: Hb ≤ 11.9 g/dL, at a dose that is reduced by two dose steps
-1.0 to 1.0	↑			↑	No change	↓	
> 1.0	No change			No change	↓	↓	

Abbreviations: ↑ = increase; ↓ = decrease; Hb = hemoglobin; wk(s) = week(s).

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, and 300 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 200 mg results in 150 mg as the new dose.

*Note: Subjects who were on the 120 mg dose step prior to Amendment 2 may still use that dose unless/until a dose review requires a change, at which point new dose steps should be implemented.

Note: Maximum dose capped at 3.0 mg/kg per dose or 300 mg, whichever is lower. Subjects on higher maximum doses from previous protocol versions must change to the new maximum dose at the next scheduled visit.

In a subject whose baseline Hb level was < 8.0 g/dL, a dose increase can be made with either a 1 or 2 dose step increase, per Investigator discretion, to minimize the risk of requiring rescue treatment.

Dose Adjustment for Excessive Hematopoiesis:
At any time during the Treatment Period:

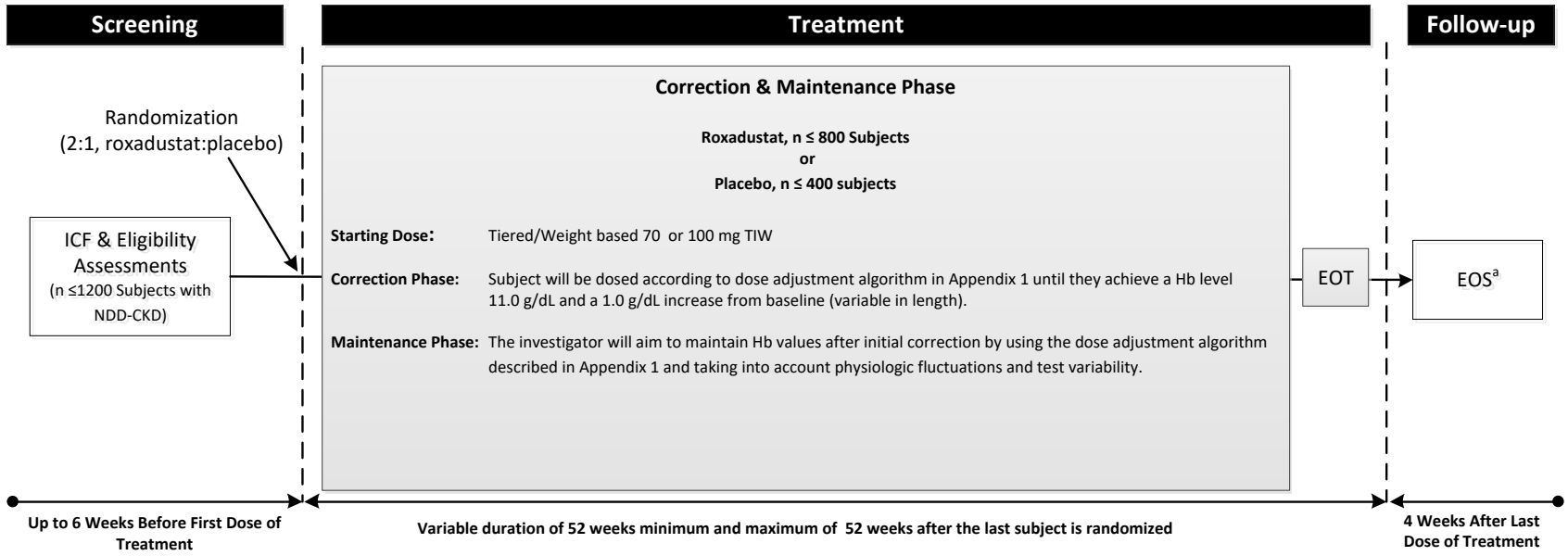
- If Hb increases by > 2.0 g/dL in ≤ 4 weeks (eg, any 4-week time period), the dose should be reduced by one dose step.

Contact the Medical Monitor if dose adjustments are required past the limits of the dose steps; ie, 20 or 300 mg.

Appendix 2 Schedule of Assessments

Study Period:	**Screening**			**Treatment**					**Follow-up**
Visit / Week:	**Up to 6 Weeks**			**Day 1 (Wk 0)**	**Weekly (Wks 1 & 2)** ± 2 days	**Every 2 Weeks (From Wks 4 to 24)** ± 2 days	**Every 4 Weeks** (Wks 28 to EOT)± 3 days	**EOT (or ET)** ± 3 days	**EOS (4wks post EOT or ET)** ± 2 days
	1	**2**	**3**						
Written informed consent	X								
Eligibility criteria	X			X					
Demographics and medical history	X								
Physical examination	X			X		Wks 12, 24	Wks 36, Q12Wk	X	X
Height, weight	X			X					
Blood pressure, heart rate, respiratory rate, temperature	X	X	X	X	X	X	X	X	X
Hemoglobin		X	X			Wk 6	X		
CBC with WBC differential	X			X	X	Wks 4, 8, 12, 20	Wks 28, Q8Wk	X	X
Serum chemistry	X			X		Wks 4, 8, 12, 20	Wks 28, Q8Wk	X	X
LFTs and CPK					Wk 2	Wks 6, 16			
Lipid panel (fasting whenever possible)	X			X		Wks 4, 8, 12, 20	Wks 28, 36, 44, 52, Q12Wk	X	X
Serum iron, ferritin, TIBC, TSAT	X			X		Wks 4, 8, 12, 20	Wks 28, Q8Wk	X	X
CHr	X			X	Wk 2	Wks 4, 6, 8, 12, 20	Wks 28, Q8Wk	X	X
HbA1c	X			X		Wk 12	Wks 28, Q16Wk	X	X
Vitamin B_{12}, folate	X								
HIV ELISA, HBsAg, anti-HCV Ab	X								
Urine hCG pregnancy test	X								
Point of care qualitative urine pregnancy test				X		Wk 12, 24,	Wk 36, Q12Wk	X	X
Reticulocyte count				X	X	Wks 8, 12, 20	Wks 44, 68, 84	X	X
Urinalysis				X					
Special laboratory analytes (hepcidin, hs-CRP)				X		Wks 4, 12, 20	Wks 44, 68, 84	X	X
Archival serum/plasma samples				X		Wks 4, 12, 20	Wks 44, 68, 84	X	X
HemoCue assessment				X	X	X	X		
Quality-of-life questionnaires				X		Wks 12	Wks 28, 52, 76	X	
12-lead ECG				X			Wks 28, 52, 76	X	
Renal ultrasound		X							
Dose adjustment					X	Wk 4, Q4Wk	X, Q4Wk		
Adverse event recording	X	X	X	X	X	X	X	X	X
Concomitant medication recording	X	X	X	X	X	X	X	X	X
Procedure and nondrug therapy recording	X	X	X	X	X	X	X	X	X
Study drug dispensing				X	X	X	X		

Appendix 3 Study Schema



Abbreviations: EOS=end of study; EOT=end of treatment; Hb=hemoglobin; ICF=informed consent form; n=number of subjects; NDD-CKD=nondialysis-dependent chronic kidney disease; TIW=three times a week.

a EOT + 4 weeks ±3 days

Appendix 4 Liver Safety Monitoring and Assessment Guidelines

The guidelines described in this section are intended to enable early detection and action following abnormal LFT results and are consistent with FDA guidance for monitoring of Drug Induced Liver Injury (DILI).

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

In addition:

Repeat LFTs within 2-3 days if:	**Discontinue Study Drug, if:**
• ALT **or** AST > 3x ULN, **or** • Tbili > 2x ULN	• ALT or AST > 8x ULN, **or** • ALT or AST > 5x ULN for > 2 weeks, **or** • ALT or AST > 3x ULN and (Tbili > 2x ULN or INR > 1.5), **or** • ALT or AST > 3x 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; Tbili = total bilirubin; ULN = upper limit of normal.

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

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

Evaluate the subject for potential causes, which may include the following:

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

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

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

Appendix 5 Sponsor Signature(s)

A Phase 3, Randomized, Double-Blind, Placebo Controlled Study of the Efficacy and Safety of Roxadustat (FG-4592) for the Treatment of Anemia in Chronic Kidney Disease Patients not on Dialysis

Protocol Number: FGCL-4592-060, Amendment 3, 20 September 2017

Signature:_____ [redacted]	Date: _____
Signature:_____ [redacted]	Date: _____