TITLE PAGE

CLINICAL STUDY PROTOCOL STUDY TITLE:	A Phase 2 Open Label Study Investigating the Efficacy and Safety of Roxadustat (FG-4592) for Treatment of Anemia in Patients Receiving Chemotherapy Treatment for Non-Myeloid Malignancies
PROTOCOL NUMBER:	FGCL-4592-092
PHASE:	Phase 2
STUDY SPONSOR:	FibroGen, Inc. 409 Illinois Street San Francisco, California 94158 USA
KEY SPONSOR CONTACT(S):	[redacted] Direct: [redacted] Mobile: [redacted] E-mail: [redacted]
IND NUMBER:	142993
STUDY DRUG:	Roxadustat (FG-4592)
INDICATION:	Treatment of Anemia Caused by Chemotherapy
ORIGINAL PROTOCOL:	02 April 2019
AMENDMENT 1:	16 July 2019
AMENDMENT 2:	30 January 2020
AMENDMENT 3:	22 May 2020

CONFIDENTIALITY STATEMENT

INVESTIGATOR SIGNATURE PAGE

STUDY ACKNOWLEDGEMENT

A Phase 2 Open Label Study Investigating the Efficacy and Safety of Roxadustat (FG-4592) for Treatment of Anemia in Patients Receiving Chemotherapy Treatment for Non-Myeloid Malignancies

FGCL-4592-092

Amendment 3: 22 May 2020

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, and any applicable local health authority, and Institutional Review Board (IRB)/Independent Ethics Committee (IEC) requirements.

Investigator Name (Printed)	Institution
Signature	Date

Please return a copy of this signature page to FibroGen (or designee). Please retain the original for your study files.

CONFIRMATION OF PROTOCOL APPROVAL

Amendment 3 Protocol Date: 22 May 2020

This protocol is approved by FibroGen.

DocuSigned by:

[redacted]

te

FibroGen, Inc.

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
Upon evaluating the pharmacodynamics (hemoglobin) responses after 4 weeks of therapy with the starting dose of 2.0 mg/kg in initial 20 patients, it has been determined to increase the starting dose for newly enrolled patients by one level i.e. from 2.0 mg/kg to 2.5 mg/kg level as majority of the initial 20 patients required a dose increase at Week 5, per dose adjustment rule.	To achieve optimal Hb response with the starting dose	Synopsis 3.3.1; 5.1; 7.1.1
Exclusion #17 was updated from: "Known, active or chronic gastrointestinal bleeding" to "Known, active or chronic ~~gastrointestinal~~ bleeding"	The criterion has been revised to exclude all types of active/chronic bleeding	Synopsis; 6.2
Section 7.1.5.2 Chemotherapy Treatments has been updated to the following (changed text is italicized): "If Paclitaxel (e.g. Taxol® or Abraxane®) is given as part of a chemotherapy regimen, roxadustat dosing should be held for *24* hours before and after treatment *(time 0 = start of infusion)* with this drug. Roxadustat dosing frequency may be adjusted, as needed."	The current suggested 48 hour interval between roxadustat and paclitaxel administration was added as a precautionary step as paclitaxel is known to have drug-drug interaction with several different drugs. However, upon further in-house review of paclitaxel PK, FibroGen considers the potential for DDI with roxadustat relatively insignificant if the interval between roxadustat and paclitaxel is reduced to 24 hours. FibroGen is reducing the 48 hour interval to 24 hours and clarifying the window start time as the start of infusion.	7.1.5.2
Paclitaxel PK sub-study has been added under Section 8.2.4.2 to evaluate the effect of roxadustat timing of administration on the pharmacokinetics of paclitaxel.	This PK sub study will help us to determine the impact roxadustat timing of administration on paclitaxel PK (drug-drug-interaction) and whether there is a need for an interval between roxadustat and	8.2.4.2

Additional details are provided in Appendix 6	paclitaxel administration to avoid drug-drug-interaction, if any, in patients who may be taking both Roxadustat and Paclitaxel concomitantly.	
Appendix 6 has been added to describe Paclitaxel PK study including instruction for collecting PK samples for patients taking Roxadustat and Paclitaxel concomitantly:	PK collection time points were defined for patients taking part in the optional sub-study investigating the potential effect of Roxadustat on the pharmacokinetics of paclitaxel.	Appendix 6
Secondary efficacy endpoints and Subgroup analysis have been revised	For better understanding the effects of roxadustat on efficacy parameters and PK properties of roxadustat and paclitaxel	Synopsis 4.2.2 4.2.5

1. PROTOCOL SYNOPSIS

PROTOCOL SYNOPSIS	
Study Title:	A Phase 2 Open Label Study Investigating the Efficacy and Safety of Roxadustat (FG-4592) for Treatment of Anemia in Patients Receiving Chemotherapy Treatment for Non-Myeloid Malignancies
Protocol Number:	FGCL-4592-092
Investigational Product:	FG-4592 (Roxadustat)
Study Phase:	Phase 2
Indication:	Treatment of Anemia Caused by Chemotherapy
Number of Patients Planned:	Up to approximately 100
Number of Sites Planned:	Approximately 10-20 (United States Only)

OBJECTIVES

Primary Objective:

- To evaluate the efficacy of roxadustat for the treatment of anemia in patients receiving multi-cycle treatments of myelosuppresssive chemotherapy.

Secondary Objectives:

- Evaluate the safety of roxadustat
- Evaluate the impact of roxadustat on RBC transfusion requirements
- Evaluate effect of roxadustat on biological indicators:, hemoglobin, hematocrit, reticulocytes, hepcidin, serum iron, ferritin, transferrin saturation and total iron binding capacity

ENDPOINTS
Primary Efficacy Endpoint: • The primary efficacy endpoint is maximum change in hemoglobin within 16 weeks from baseline without RBC transfusion

Secondary Efficacy Endpoints:

- Mean change in hemoglobin from baseline to week 16 (without RBC transfusion)
- Change in hemoglobin from baseline at) week 8, 12, 16 (without RBC transfusion)
- Proportion of patients who achieved a ≥1 g/dL increase in hemoglobin from baseline through week 16
- Time to achieve a ≥1 g/dL increase in hemoglobin from baseline
- Proportion of patients who achieved a ≥1.5 g/dL increase in hemoglobin from baseline through week 16
- Proportion of patients who achieved a hematopoietic response at any time in the study (defined as an increase in Hb of 1.5 g/dL OR attaining a Hb of 11 g/dL)
- Proportion of patients who achieved a ≥2.0 g/dL increase in hemoglobin from baseline through week 16
- Number (%) of patients who had a RBC transfusion from beginning of Week 5 (Day 29) to week 16

Additional Efficacy Endpoints:

- Proportion of patients who achieved a ≥1 g/dL increase in hemoglobin from baseline through week 8 and 12
- Proportion of patients who achieved a ≥1.5 g/dL increase in hemoglobin from baseline through week 8 and 12
- Number (%) of patients who require transfusion as medical intervention and/or ESA (erythropoiesis stimulating agent) as a rescue agent. [Time Frame: baseline to week 16]
- Percentage of Participants by Tumor Type With Improvement in FACIT-F (fatigue) and Increase in Hemoglobin ≥1 g/dL [Time Frame: baseline to week 16]
- Change from Baseline in Quality of life as measured by:

  Functional Assessment of Cancer Therapy-Anemia (FACT-An) test [Time Frame: baseline to week 8 and 16]

Exploratory Evaluations:

- Effect on hepcidin and iron metabolism
- Effect on cholesterol parameters and lipid metabolism

Subgroup Analyses:

- Tumor type
- Chemotherapy regimen [i.e. platinum vs non-platinum]
- Other clinically relevant characteristics
- Roxadustat PopPk

- Paclitaxel DDI

STUDY DESIGN

This is a Phase 2 Open Label Study Investigating the Efficacy and Safety of Roxadustat (FG-4592) for Treatment of Anemia in Patients Receiving Chemotherapy Treatment for Non-Myeloid Malignancies. Approximately 100 patients will be enrolled.

STUDY PERIODS

Screening Period:

All screening procedures are to be completed within 28 days prior to Study Day 1. Patients will be evaluated per the protocol inclusion/exclusion criteria to determine eligibility for participation in this trial. Protocol assessments will be completed during screening visits in accordance with Schedule of Assessments (SOA) to establish a baseline profile, including; demographics, medical history, clinical status and disease stage for each patient. Patients determined to be eligible for participation will be enrolled in the trial and will receive roxadustat in an open-label manner. The starting dose for the initial 20 patients will be 2.0 mg/kg. After the initial 20 patients are enrolled, starting dose(s) for additional patients will be selected by the sponsor, informed by the data available from earlier patients treated in the study. The selected starting dose level will not exceed the highest dose level received by any individual patient in the study up to that point and will be within the maximum dose allowed in the protocol. Additionally, the sponsor will review clinical efficacy and safety response on an ongoing basis and take into account potential impact of certain baseline patient characteristics or chemotherapy regimens (such as from patients on a platinum vs non-platinum containing regimen) on treatment response in the selection of patients of baseline characteristics and starting dose(s) of subsequent patients. Lastly, if there is more than one starting dose cohort open for enrollment at the same time for a certain subgroup, such as platinum (or non-platinum) treatment group, patients will be randomized to receive a starting dose. A comprehensive table of potential doses is contained in the protocol body and in Appendix 2.

Upon evaluating the pharmacodynamics (hemoglobin) responses after 4 weeks of therapy with the starting dose of 2.0 mg/kg in initial 20 patients, it has been determined to increase the starting dose for newly enrolled patients by one level i.e. from 2.0 mg/kg to 2.5 mg/kg level to achieve optimal hemoglobin response.

Treatment Period:

Patients will undergo 16 weeks of study treatment with roxadustat. Study visits are scheduled every 2 weeks. Patients' clinical status and safety will be regularly evaluated. Efficacy assessments will be performed routinely to evaluate patients' quality of life and disease state. If disease progression occurs during the treatment period, patients will be discontinued from study treatment and continue in the follow-up period.

Follow-up Period:

All patients who complete 16 weeks (of treatment with study medication) will undergo a 4-week follow-up period after the last dose of study medication.

Patients who discontinue study medication early (for any reason whatsoever) will have a 4-week follow-up visit after stopping study medication.

PATIENT ELIGIBILITY CRITERIA

Inclusion Criteria:

1. Diagnosis of non-myeloid malignancy. Current documentation of disease burden (e.g. CT scan) within 3 months prior to enrollment (Day 1).
2. Anemia caused by cancer treatment (myelosuppressive chemotherapy) defined as Hb ≤10.0 g/dL at screening
3. Planned concurrent treatment of cancer (myelosuppressive chemotherapy) for at least 8 additional weeks
4. Age ≥ 18 years
5. Body weight ≥ 45 kg and < 150 kg
6. ECOG performance status of 0, 1, or 2 at last screen visit
7. Patient must be capable of giving written informed consent
8. Understand and sign informed consent; be willing to comply with all study procedures
9. Estimated life expectancy ≥ 6 months at enrollment (Day 1)

Exclusion Criteria:

1. Patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure
2. Patients who are only receiving hormonal products, biological products, novel immunosuppressive products (such as PD-1 and PD-L1 checkpoint inhibitors) or targeted biological or radiation therapy to treat/manage their cancer. (Patients receiving concomitant myelosuppressive therapy if not intended for cure may be allowed to participate)
3. Patients who prefer a Red Blood Cell (RBC) transfusion as treatment of anemia at time of study entry, over receiving the investigational drug Roxadustat
4. Received an RBC transfusion or ESA within 4 weeks of enrollment (Day 1)
5. Alanine aminotransferase (AST) > 3 x upper limit of normal (ULN), OR aspartate aminotransferase (ALT) > 3 x ULN, OR total bilirubin (TBL) > 1.5 x ULN – will exclude a patient from entering the study (patients with TBL up to 2x ULN may be allowed if ALT/AST are within normal limit and investigator has no safety concerns)
6. Inadequate iron stores as defined as ferritin < 50 ng/mL
7. Any investigational drug within 8-weeks prior to Day 1 Treatment or plans to use any of these medications during the course of clinical trial participation
8. Anticipated use of dapsone during the study

9. Clinically significant anemia due to other etiologies such as iron deficiency, vitamin B_{12} or folate deficiency, autoimmune or hereditary hemolysis or anemia, hemorrhage, or hereditary anemia such as sickle cell anemia or thalassemia
10. Active infection(s) requiring chronic antibiotic therapy
11. Estimated Glomerular Filtration Rate (eGFR) < 30 mL/min based on 4-variable MDRD equation
12. Thromboembolic event (deep vein thrombosis (DVT), pulmonary embolism, myocardial infarction, stroke, transient ischemic attack (TIA) within previous 6 months of screening
13. Significant heart disease, including New York Heart Association (NYHA) Class III or IV congestive heart failure, uncontrolled hypertension or hypotension, or significant valvular or endocardial disease that would put the patient at risk for thromboembolism
14. Clinically significant or uncontrolled ongoing inflammatory/autoimmune disease (e.g., rheumatoid arthritis, Crohn's disease, celiac disease, etc.)
15. History of significant liver disease or active liver disease
16. Major surgery planned during the treatment period
17. Known, active or chronic bleeding
18. Known human immunodeficiency virus (HIV), hepatitis B or hepatitis C infection
19. Clinically significant or uncontrolled medical condition that would affect the patient's ability to participate in the study or confound the study's efficacy or safety results
20. History of leukemia (current or historical Chronic Lymphocytic Leukemia may be allowed)
21. Previous recipients of roxadustat or another hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI)
22. Pregnant or breastfeeding females

STUDY TREATMENT

Dose and Mode of Administration:

Roxadustat:

Tablets with strengths of 20 mg, 50 mg ,100 mg and 150 mg

Route of Administration:

Oral (all tablets must be administered whole).

Patients will receive roxadustat, at a starting dose of 2.0 mg/kg TIW with actual dose (in mg) based on body weight at Day 1 of treatment, per table below.

Starting dose for initial 20 patients:

Dose Level Group	Roxadustat Dose Level (mg/kg)	45 to < 70 kg	70 - 100 kg	> 100 kg
1	2.0	100 mg TIW	150 mg TIW	200 mg TIW

Starting dose for newly enrolled patients:

Upon evaluating the pharmacodynamics (hemoglobin) responses after 4 weeks of therapy with the starting dose of 2.0 mg/kg in initial 20 patients, it has been determined to increase the starting dose for newly enrolled patients by one level i.e. from 2.0 mg/kg to 2.5 mg/kg level to achieve optimal hemoglobin response.

Dose Level Group	Roxadustat Dose Level (mg/kg)	45 to < 70 kg	70 - 100 kg	> 100 kg
1	2.5	150 mg TIW	200 mg TIW	250 mg TIW

Dose adjustment evaluation will be made every 4 weeks, and dose will be titrated to Hb level and rate of Hb change according to Appendix 2.

Principal Investigator (PI) and/or treating physician will determine when to transfuse a patient based on clinical judgement.

Evaluation for dose modification/adjustment will occur every 4 weeks. Any potential dose escalation/dose reduction will be at pre-defined dose step increments.

After the initial 20 patients are enrolled, starting dose(s) for additional patients will be selected by the sponsor, informed by the data available from earlier patients treated in the study. The selected starting dose level will not exceed the highest dose level received by any individual patient in the study up to that point and will be within the maximum dose allowed in the protocol.

Additionally, the sponsor will review clinical efficacy and safety response on an ongoing basis and take into account potential impact of certain baseline patient characteristics or chemotherapy regimens (such as from patients on a platinum vs non-platinum containing regimen) on treatment response in the selection of patients of baseline characteristics and starting dose(s) of subsequent patients. Lastly, if there is more than one starting dose cohort open for enrollment at the same time for a certain subgroup, such as platinum (or non-platinum) treatment group, patients will be randomized to receive a starting dose. A comprehensive table of potential doses is contained in the protocol body and in Appendix 2. Finally, starting doses will not be adjusted for platinum containing or non-platinum containing regimens until 8 patients in a group have been dosed at a specific dose level.

In the event that chemotherapy is modified or withheld or discontinued, as per standard of care, the dosing schedule of roxadustat should be maintained through the 16 week treatment period, and patients will continue in the follow-up period.

Other Important Information:

Best supportive care (BSC) including RBC transfusion is permitted to ensure patient's safety. Principal Investigator (PI) and site staff will utilize their own institutional criteria to determine when to transfuse a patient.

Use of any ESA during the study (epoetin alfa, epoetin beta, darbepoetin, Mircera, or others; see Appendix 5) is not permitted. Patients who receive an ESA will be discontinued from further treatment with study medication.

See the Investigator's Brochure for additional information pertaining to roxadustat.

STATISTICAL METHODS

The sample size of the study was not determined by formal power calculations. All analyses will be exploratory for different dose level.

The following analysis populations are defined and will be used for the statistical analysis:

- All enrolled or ITT: consisted of all patients enrolled in the roxadustat treatment period, regardless of whether patients received any roxadustat.
- Full analysis set (FAS): consisted of all enrolled patients who receive at least one dose of roxadustat, have a baseline Hb and at least one corresponding on-treatment Hb assessment, and will be used for all efficacy analyses
- Efficacy Evaluable (EE): consisted of all enrolled patients who receive at least one dose of roxadustat for at least 4 weeks, and have at least one Hb value after 4 weeks or longer, obtained within 2 weeks of last dose.
- Safety Population (SAF): consisted of all patients who received at least one dose of roxadustat. This population will be for all assessments of safety and tolerability

The efficacy analysis will be based on both the Full Analysis Set (FAS) population and Efficacy Evaluable (EE) Population.

Analyses of the safety data will be based on the Safety Population.

Baseline Hb value for efficacy analysis is defined as the mean of Screening (central laboratory) Hb values and Day 1 (central laboratory) Hb value.

Data Analyses

Up to approximately 100 patients will be enrolled in the study, with various diagnoses of non-myeloid malignancies.

Primary efficacy analysis

The primary efficacy analysis will be based on the EE and FAS population using an observed data approach. The primary efficacy parameter is defined as maximum change in hemoglobin in 16 weeks without RBC transfusion.

Maximum Change from baseline will be summarized by using descriptive statistics. Maximum change from baseline will also be analyzed using Analysis of covariance using cancer types as a class variable and the baseline Hb as a covariate. Least Square Means will be calculated from the model and tested against 0 for each cancer type and overall.

Secondary efficacy analyses

The mean change from baseline hemoglobin (without a RBC transfusion) will be summarized using descriptive statistics by visit. This will also be analyzed similar to the model used for the primary endpoint.

In addition, missing hemoglobin data, either because of a missed visit or collected within 4 weeks after a RBC transfusion will be imputed with the last-observation-carried-forward (LOCF) approach.

The Number (%) of patients meeting various criteria specified in the protocol as secondary endpoints will also be summarized using the Clopper–Pearson confidence limits approach.

The percentages of patients who have a hematopoietic response, who receive at least one RBC transfusion will be estimated using the Kaplan–Meier (KM) method.

Safety Analysis

Adverse events, laboratory, vital signs, ECGs data will be descriptively summarized and/or listed. Change from baseline values may be calculated for selected vital sign and ECG parameters. Shift tables may also be constructed.

Additional endpoints may be detailed with corresponding statistical analysis methods specified in a Statistical Analysis Plan (SAP).

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.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
~	Approximately
AB	Antibody
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
BM	Bone Marrow
BP	Blood Pressure
BSC	Best Supportive Care
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CHr	Reticulocyte Hemoglobin Content
CIA	Chemotherapy Induced Anemia
CKD	Chronic Kidney Disease
C_{max}	Maximum Concentration
CRF	Case Report Form
DD	Dialysis-dependent
DVT	Deep Vein Thrombosis
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
ECG/EKG	Electrocardiogram
EE	Efficacy Evaluable
EOT	End of Treatment
EPO	Erythropoietin
ESA	Erythropoiesis-stimulating Agent
ESRD	End-stage Renal Disease
FACT-An	Functional Assessment of Cancer Therapy-Anemia
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue

FAS	Full analysis Set
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyl Transferase
Hb	Hemoglobin
HBsAg	Hepatitis B Surface Antigen
hCG	Human Chorionic Gonadotropin
HCT	Hematocrit
HCV	Hepatitis C Virus
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
IU	International Unit
IV	Intravenous
LDH	Lactate Dehydrogenase
LLN	Lower Limit of Normal
LFT	Liver Function Test
LOCF	Last Observation Carried Forward
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MDRD	Modification of Diet in Renal Disease
MDS	Myelodysplastic Syndromes

MedDRA	Medical Dictionary for Regulatory Activities
N	Sample Size
PD	Pharmacodynamics
PI	Principal Investigator
PK	Pharmacokinetics
PRO	Patient Reported Outcome
PTT/PT	Prothrombin Time/Partial Thromboplastin Time
QOL	Quality of Life
RBC	Red Blood Cell
RR	Respiratory Rate
SAE	Serious Adverse Event
SAF	Safety Population
SAP	Statistical Analysis Plan
SoA	Schedule of Events
Tbili	Total Bilirubin
TEAE	Treatment-emergent Adverse Event
TESAE	Treatment-emergent Serious Adverse Event
TIA	Transient ischemic Attack
TIBC	Total Iron Binding Capacity
TIW	Three Times Weekly
TSAT	Transferrin Saturation
UIBC	Unsaturated Iron-binding Capacity
ULN	Upper Limit of Normal
VEGF	Vascular Endothelial Growth Factor
WBC	White Blood Cell

3. INTRODUCTION

Roxadustat (the investigational study drug) is a new chemical entity (NCE) which belongs to a new pharmacological class of small molecule enzyme inhibitors (hypoxia inducible factor prolyl hydroxylase inhibitor, HIF-PHI). It is a potent and reversible inhibitor of the prolyl hydroxylase enzymes that regulate the stability of the hypoxia-inducible factor (HIF) for regulation of erythropoiesis. Roxadustat has been investigated for the treatment of CKD anemia in multiple phase 2 studies and phase 3 studies, and all consistently showed robust efficacy and acceptable safety profile to date. Furthermore, when roxadustat was tested in a rodent model of chemotherapy induced anemia, it was efficacious. In light of the unmet medical need in Chemotherapy-Induced Anemia (CIA) where patients have limited choices all of which are suboptimal, we aim to develop a new therapeutic option. This study proposes to evaluate the use of roxadustat in the treatment of Chemotherapy-Induced Anemia.

3.1. Chemotherapy Induced Anemia (CIA)

Chemotherapy-Induced Anemia is anemia from reduction in red blood cell production by the bone marrow due to myelosuppression by chemotherapeutic agents. The anemia due to myelosuppressive effect of chemotherapy leads to a decrease in patient's hemoglobin level. As oxygen is critical to survival of all cells in the body, a reduction in oxygen-carrying capacity, measured as low Hb level, can have significant impact on the function of various organs and risks depending on the severity of anemia. The most common manifestations of anemia are fatigue, low energy, and poor quality of life. In severe cases of CIA when the anemia becomes life-threatening, blood transfusion may be given if available; in this case, the patient may be subjected to the risk of infection and/or immunogenic reactions associated with RBC transfusion. Patient outcome could be compromised if the dose and frequency of chemotherapeutic regimen were to be reduced in order to reduce its myelosuppressive effects to address the severe anemia.

3.1.1. Epidemiology of Chemotherapy Induced Anemia

Anemia is one of the most common consequences of chemotherapeutic agents where incidence of anemia is over 60% and prevalence is 30% to 90% in the same patient population particularly in those patients undergoing multiple rounds of chemotherapy. The incidence and severity of chemotherapy-related anemia depend on a variety of factors, including (but not limited to) the type of chemotherapy, schedule and intensity of therapy administered. Other factors are whether the patient has received prior myelosuppressive treatment, radiation therapy or both. There is relatively higher incidence of mild-to-moderate than severe anemia. However, elderly cancer patients may show higher severity of clinical symptoms of anemia even at higher hemoglobin levels than do younger people or anemic patients without cancer. Retrospective reviews of incidence of anemia that required RBC transfusions in patients with nonmyeloid malignancies who received cytotoxic chemotherapy indicate that the highest frequency occurs in those patients with lymphomas, lung tumors, and gynecologic (ovarian) or genitourinary tumors in which the incidence may be as high as 50%-60%. The proportion of anemic (hemoglobin <11 g/dL) patients increased from 17% before the first chemotherapy cycle to 35% by the sixth cycle of treatment, with 49% and 51% of the patients with ovarian and lung tumors, respectively, anemic by the sixth cycle of chemotherapy. The mean hemoglobin concentration at which a transfusion was given decreased progressively with each treatment cycle.

3.1.2. Etiology of Chemotherapy Induced Anemia

Chemotherapeutic agents induce anemia through directly impairing hematopoiesis, including synthesis of RBC precursors, in the bone marrow. In addition, nephrotoxic effects of particular cytotoxic agents (e.g., platinum-containing agents) can also lead to anemia through decreased renal production of erythropoietin. Platinum-based regimens, commonly used in lung, ovarian, and head and neck cancers, are well known to induce anemia caused by combined bone marrow suppression and kidney toxicity. The myelosuppressive effects of some cytotoxic agents are likely to accumulate over the course of repeated cycles of treatments, resulting in a steady worsening of anemia with additional chemotherapy cycles. An increase in the fraction of grades 2 and 3 anemia was associated with increasing number of chemotherapy cycles.

3.1.3. Clinical Features of Chemotherapy Induced Anemia

Anemia is a common cause of morbidity in cancer. Because anemia of chronic disease is prevalent in cancer patients, mild anemia is common before initiation of treatment. Anemia generally worsens over time, over repeated cycles of cytotoxic chemotherapies. The anemia associated with chemotherapy are normochromic, normocytic but with inappropriately low reticulocyte count. Serum Iron and Iron-binding capacity are low. Bone marrow (BM) morphology reveals normal erythroid precursor with normal or slightly increased stainable iron. Erythroid progenitors (BFU-E & CFU-E) size, number and degree of hemoglobinization are normal while the BM still maintains normal sensitivity to erythropoietin (EPO). CIA is characterized by decrease in hemoglobin (Hb) concentration, RBC count and / or packed cell volume to subnormal levels.

3.1.4. Current Treatment of Chemotherapy Induced Anemia

The current treatment options for CIA are limited, and thus the anemia in most patients with CIA remain untreated. Although ESA has been approved for the treatment of CIA, its use has decreased precipitously due to safety concerns of risk of tumor progression, death, and cardiovascular risk. Such risks are associated with the high doses of ESA used in CIA (about 3X to 5X of doses for CKD anemia). RBC transfusions are sometimes used for treating severe CIA, but patients would be exposed to the risks of infection and immunogenic reactions associated with RBC transfusions. Reduction in chemotherapy use may decrease the myelosuppressive effects, but patients' outcome could also be compromised. Given the limitations in the current choices, a new efficacious, safe, and convenient treatment option for CIA is needed.

3.2. Roxadustat

3.2.1. Mechanism of Action of Roxadustat

Roxadustat (FG-4592) is an orally administered inhibitor of HIF-PHI. FG-4592 increases cellular levels of HIF. 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 the acute and chronic responses to hypoxia. In addition, HIF-responsive genes regulate a wide range of processes, including erythropoiesis, iron metabolism, oxidation, cellular metabolism, glycolysis, vasculogenesis, cell cycle progression, and apoptosis.

FG-4592 is a potent and reversible HIF-prolyl hydroxylase inhibitor 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. Thus, FG-4592 pharmacologically stimulates erythropoiesis through the HIF pathway and in a manner consistent with the body's normal homeostatic response to anemia, but under normal oxygenation conditions.

The physiologic mechanisms underlying the effects of FG-4592 on erythropoiesis are distinct from that of ESAs. These differences result in several potential advantages over ESAs beyond the convenience of oral therapy, including:

- Transient increase of circulating endogenous erythropoietin levels at or near physiologic levels
- Improved iron metabolism and bioavailability
- Effective erythropoiesis in the presence of inflammation
- Increase in the number of EPO receptors in the bone marrow
- Improvement in lipid profile

3.2.2. Clinical Experience with Roxadustat

A total of 22 Phase 2 and 3 clinical efficacy and safety studies have been completed and three studies are ongoing at the time of this submission. As of the 07 September 2019 data cut-off, 13063 patients (943 healthy patients, 5994 patients with NDD-CKD, and 6126 patients with DD-CKD) have been randomized in the roxadustat CKD clinical development program. An estimated total of 7821 patients received roxadustat, 3129 patients received active comparator (epoetin alfa or darbepoetin alfa), and 2113 patients received placebo. Over 11,000 subjects have enrolled into Phase 3 studies.

There are > 3200 CKD patients exposed to roxadustat for >= 1 year, and of whom about half have received roxadustat for >=2 years. There is a small number of patients receiving roxadustat for > 5 years. Long term studies suggest durability of erythropoietic effect. There have been no safety concerns to date, inclusive of thorough QT study which tested roxadustat dose up to 5 mg/kg in healthy volunteers, with no evidence of QTc prolongation. The anemia correction response rates in anemic CKD patients not on dialysis (Studies FGCL-4592-041, FGCL-4592-047, FGCL-4592-808) and those starting dialysis therapy (FGCL-4592-053, ASP-1517-CL-302) were >90%.

Roxadustat has also been shown to maintain Hb levels when ESA has been withdrawn in dialysis-dependent (DD) end stage renal disease (ESRD) patients who previously depended on ESA for Hb maintenance (Studies FGCL-4592-040, FGCL-4592-048, FGCL-4592-806, and ASP-1517-CL-307). In CKD patients, the roxadustat dose requirement and achieved Hb levels are not impacted by baseline C-reactive protein level (CRP), a measure of inflammation, which is suggestive of roxadustat's ability to overcome the dampening effect of inflammation on erythropoiesis (FGCL-4592-053, FGCL-4592-806).This is a challenge for ESA use for anemia in inflamed patients as higher ESA dose was used and the Hb level achieved were still lowered in patients with elevated CRP in study 808. Anemia of inflammation affects various patient

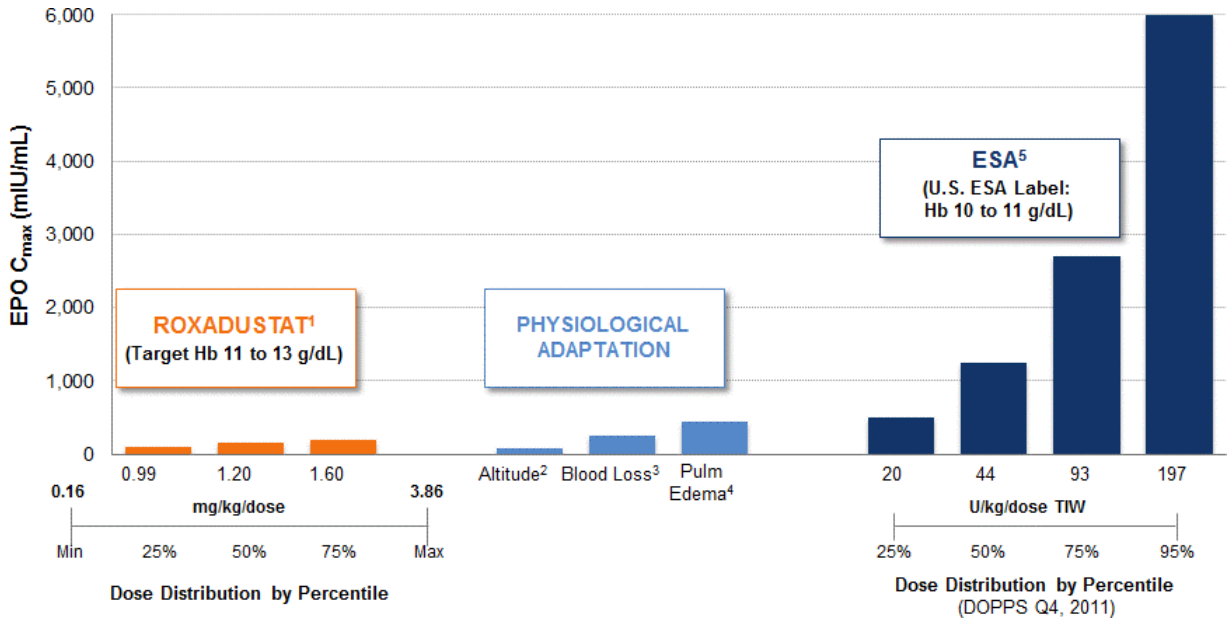
populations with chronic diseases, including those with cancer. Roxadustat also overcomes the iron dysregulation in CKD patients to enable iron utilization for erythropoiesis, by reducing the hepcidin level, and also lowering serum ferritin levels.

Comprehensive safety information can be found in the Investigator's Brochure.

3.2.3. Pharmacology (PK/PD) of Roxadustat

Supra-physiological recombinant human erythropoietin (rhEPO) levels may be a contributing factor in the increased cardiovascular and thrombotic risk observed in ESA treated CKD patients and the very high doses of ESA required (up to five times the dose required in anemia associated with CKD) potentially contribute to ESA's cancer progression risks in oncology patients. Roxadustat, a HIF-PHI mechanism impacting multiple parts of the erythropoietic pathway, has been shown to expose CKD patients to much lower plasma EPO levels than ESA when achieving comparable erythropoietic effects, and the transient peak levels of EPO level with roxadustat doses used in CKD patients are within the range of physiologic adaptation. Figure 1 depicts the impact of environment on plasma EPO levels: with a range from 10 to 15 mIU/mL in healthy patients at sea level, while EPO levels triggered by physiologic adaptation to phlebotomy are in the range of 15 to 250 mIU/mL (Goldberg, 1993, Maeda, 1992), and adaptation to moderate high altitude (4500 m) showed mean levels up to 70 mIU/mL (Milledge, 1985), to doses used in CKD patients on dialysis (far right). The off-label ESA use for treatment of anemia in MDS patients are typically at doses comparable to the EPO hypo-responsive ESRD-dialysis patients (such as those at or above the highest dose quartile in Figure 1) that leads to two orders of magnitude above the normal physiologic range of EPO. Exposure to high ESA levels are thought to be associated with higher risks to off-target effects of ESA. Roxadustat has a potential to address anemia need with more physiologic EPO exposure.

Figure 1. Circulating EPO Exposure with Roxadustat-treated CKD & ESRD Patients versus Reported ESA Dosing Patterns in ESRD 2005 and 2009



[1]C_{max} data for roxadustat estimated for a subset of 243 patients who achieved Hb response and were dosed at expected therapeutic doses; [2]Milledge & Cotes (1985); [3]Goldberg et al. (1993), Maeda et al. (1992); [4] Kato et al. (1994); [5]Based on Flaharty et al. (1990)

Furthermore, the roxadustat intermittent dosing regimen (three times weekly, TIW) enables the HIF system to reset before the next round of stabilization which enhances the durability of its therapeutic effect by avoiding tachyphylaxis while minimizing the risk of off-target effects on the HIF biology.

3.3. Rationale for Roxadustat in Chemotherapy Induced Anemia

The unmet medical need with CIA exists because of the unintended side-effect of anemia induced by chemotherapy's effect on bone marrow suppression. However, the treatment options to address CIA are limited. Of the 3 options, RBC transfusion, ESA which leads to supraphysiologic levels of endogenous erythropoietin, and/or dose reduction of the chemotherapy treatments, each has its major shortcoming. Therefore, in the US, CIA is left mostly untreated and RBC transfusion has become patients' last resort.

Roxadustat has the potential to address this unmet medical need in light of its positive efficacy demonstrated in multiple phase 2 and some phase 3 studies, with acceptable safety profile. The results from the preclinical model using cisplatin induced anemia suggest roxadustat has the potential for CIA therapy.

This study is an open label study investigating the efficacy and safety of roxadustat (FG-4592) for the treatment of anemia in patients receiving multiple cycles / rounds of chemotherapy treatments for Non-Myeloid malignancies. This will include anemic patients, with Hb ≤ 10 g/dL, in those who may require RBC transfusion, with treatment duration of 16 weeks. The primary efficacy will be evaluated after 16 weeks of treatment (Appendix 1– Schedule of Assessments).

3.3.1. Rationale for Roxadustat Dose and Dosage Regimen

For the treatment of anemia in patients undergoing multiple rounds of chemotherapy, roxadustat will be administered orally three times per week (TIW) and its dose will be titrated to achieve the target response. This study will provide the information for selection of optimal starting dose of roxadustat. In anemia therapy, the goal is to increase Hb level to ~ 11 +/- 1 g/dL. Dose requirement is individualized, and dose titration will be needed to optimize treatment results. Roxadustat dose selection in CIA is informed by the learnings from CKD anemia preclinical and clinical trials experience. The roxadustat dose shown effective in preclinical CIA model is the same as the dose used in the 5/6 nephrectomy preclinical model of CKD anemia. The starting dose of ~ 2.0 mg/kg in the first 20 patients in this study is one that is efficacious in about 80% of CKD patients, and no safety concern observed. After every 4 weeks of treatment at a dose level of roxadustat, dose requirement will be evaluated and dose modification will be made according to Appendix 2. The maximum permitted dose will be the same as that allowed in the CKD program of 400 mg or 3.5 mg/kg TIW (whichever is lower). The highest roxadustat dose studied in healthy volunteers is 5.0 mg/kg in TQT study, and there was no safety concern. There has not been a maximal tolerated dose in this program.

Upon evaluating the pharmacodynamics (hemoglobin) responses after 4 weeks of therapy with the starting dose of 2.0 mg/kg in initial 20 patients, it has been determined to increase the starting dose for newly enrolled patients by one level i.e. from 2.0 mg/kg to 2.5 mg/kg level to achieve optimal hemoglobin response. The maximum permitted dose will remain the same i.e. 400 mg or 3.5 mg/kg TIW (whichever is lower).

3.3.2. Risks/Benefit Assessment of Roxadustat Treatment in This Study

Patients with anemia have a shortage of oxygen carrier, hemoglobin. Depending on the severity of anemia, CIA can lead to fatigue, poor QOL, and when severe, it could be life-threatening. Thus, interventions such as blood transfusions, ESA use, or modification of chemotherapy regimen could be chosen by treating physicians in the management of cancer patients with CIA. Yet, each of these intervention has its inherent risks: blood transfusion carries risks of transfusion reaction, infection, and there may be limitation of blood supply; ESA use is associated with documented increased risk of death, MI, stroke, and tumor progression; and reduction in chemotherapy doses could lead to less favorable outcome for the patient. It is important to highlight that the risk with ESA in treatment of CIA is related to the very high doses required in cancer patients who suffer from myelosuppression superimposing on their varying degrees of anemia of inflammation where ESA is ineffective. The tumor progression risks and CV risks of ESA are associated with exposure to the high concentrations of exogenous recombinant EPO in the blood, at orders of magnitude above physiologic range.

The potential benefits of roxadustat include halting the reduction in Hb level and correction of anemia, thus reduction of pRBC transfusions, and avoiding the need to alter planned chemotherapy regimen to enable patients to maximal benefit of treatment. These altogether will result in the relief of signs and symptoms associated with anemia, the avoidance of the risks associated with RBC transfusions, improvement in quality of life for these cancer patients, and achieving the benefit from the optimal dose of chemotherapy treatment. In contrast to ESA, patients are exposed to endogenous erythropoietin at levels at or near physiologic range to avoid

the ESA-dose related risks, and roxadustat is expected to be efficacious regardless of inflammation as observed in CKD studies. Roxadustat is expected to overcome the inhibitory effect of inflammation of chronic disease on erythropoiesis, improve erythropoietic progenitor cells' response to erythropoietin, facilitate the mobilization of iron and ultimately lead to improved erythropoiesis. Furthermore, oral route of administration of roxadustat offers convenience to patients.

In the experience of roxadustat for treatment of CKD anemia, it has been found well tolerated and highly efficacious in a number of phase 2 and phase 3 studies. New Drug Applications have been submitted to China and to Japan. Adverse events profile is provided in the IB. This will be the first study of roxadustat for treatment of CIA for proof of concept and for dose selection. Given the extensive clinical experience with roxadustat for treatment of CKD anemia with encouraging efficacy and safety data, in addition to the positive preclinical data from CIA animal models, we believe the benefit of testing roxadustat in patients with CIA in this study far outweighs the risks. We believe roxadustat has the potential to address the unmet medical need in patients suffering from CIA.

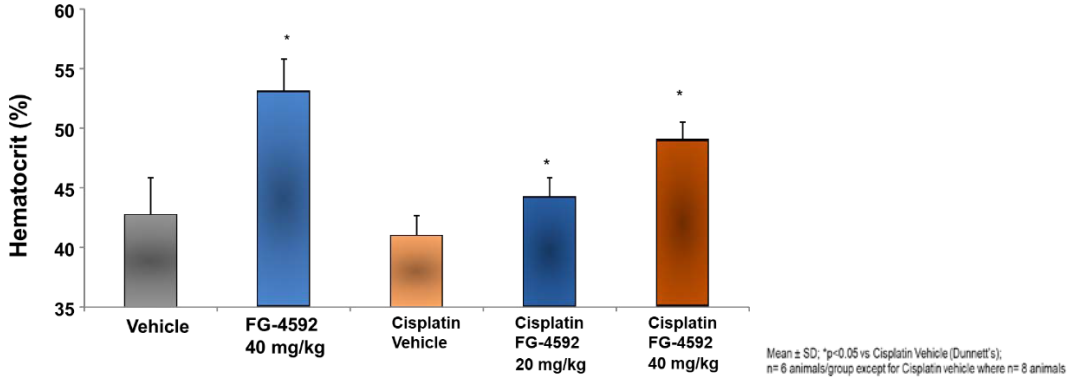
3.4. Nonclinical Studies

In addition to the usual preclinical toxicology studies to support human use of roxadustat, a number of preclinical studies have been conducted for the evaluation of efficacy of roxadustat for treatment of CIA and studies were also conducted for the assessment of safety especially in the oncology setting.

3.4.1. Roxadustat in Cisplatin-induced-anemia in Sprague Dawley Rats

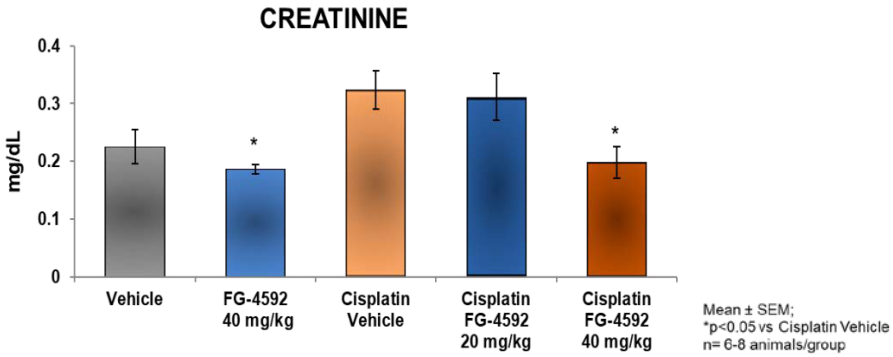
A single dose of cisplatin was administered IV on day 0 and roxadustat was administered via oral gavage on days 0, 2, 4, 7, 9, and 11 with the first dose given ~2 hours before cisplatin to Sprague Dawley rats. The treatment arms included vehicle, roxadustat 20 mg/kg or 40 mg/kg, dose response in anemia correction was noted on Day 14, per figure 2 below.

Figure 2. Roxadustat in Cisplatin-induced-anemia Response



Furthermore, roxadustat may mitigate nephrotoxic effect of cisplatin based on serum creatinine levels per Figure 3 below.

Figure 3. Roxadustat in Cisplatin-induced-anemia Creatinine Levels



It appears roxadustat can treat cisplatin induced anemia and reduce the nephrotoxic effect of cisplatin in this rodent model.

3.4.2. Preclinical Tumor Models

To assess the potential cancer risk of roxadustat, 12 tumor studies in rodents with roxadustat had been completed. These studies included xenograft, syngeneic, or spontaneous tumors of lung, colon, breast, pancreas, of ovarian, renal, prostate and leukemic origin, and melanoma, several of which are reported to be dependent on vascular endothelial growth factor, or VEGF, a protein that can be regulated by HIF for which increased levels have potentially been linked to increased tumor growth. The doses of FG-4592 used in these studies ranged from 6 to 80 mg/kg, up to 5 times the high dose in Phase 3 (2.5 mg/kg). No effect on tumor promotion was observed with roxadustat in any of the studies. In addition, roxadustat had no effect on tumor initiation or metastasis in the studies in which these end-points were also measured. Five other HIF-PH inhibitors from our HIF-PHI library have been evaluated in many of the same rodent tumor models as roxadustat, as well as some additional ones (35 studies of six HIF-PH inhibitors in 18 models total), with no observed effect on tumor initiation, promotion or metastasis.

Specifically, no tumor-related findings were observed when FG-4592 was evaluated in a VEGF-sensitive mouse model of spontaneous breast cancer. Intermittent treatment of FG-4592 and another HIF-PH inhibitor, FG-4497, were evaluated in the MMTV-Neundl-YD5 (NeuYD) transgenic mouse model of breast cancer, in which a significant elevation in markers of erythropoiesis were observed without any evidence of promotion of tumor initiation, progression, or metastasis (Seely 2017).

Finally, no significant increases in plasma VEGF levels have been observed in any of our nonclinical studies at clinically relevant erythropoietic doses of roxadustat.

3.4.3. Carcinogenicity Studies

Results of genotoxicity and 2-year rodent carcinogenicity studies showed FG-4592 to be both nonmutagenic and noncarcinogenic and thus likely a low risk for carcinogenic potential.

In genotoxicity studies, FG-4592 demonstrated no mutagenic potential in the mouse micronucleus assay or in the presence or absence of metabolic activators (S9 fraction) as tested in the bacterial reverse mutation (five Escherichia or Salmonella strains) assay and in the chromosomal aberration assay.

Two-year repeat oral TIW administration of FG-4592 to mice and rats produced no adverse effects on survival or evidence of a carcinogenic effect using up to and including the highest doses administered, 60 mg/kg and 10 mg/kg in mice and rats, respectively. Exposure levels (Cmax and AUC) of FG-4592 in the 2-year rodent bioassays were greater than in the human plasma collected from the healthy human volunteer clinical trial FGCL-4592-016. Based on the in vitro FG-4592 protein binding ratios in mice and rats which were demonstrated to be lower than in humans, the free (non-protein bound) exposure multiples between exposure at the NOAELs in the rodent studies and at the highest dose administered in the repeated dose clinical trial would be greater (~10 and 2 times higher) in mice and rats respectively based on in vitro free fraction than those estimated using total drug exposure.

3.4.4. Preclinical Safety Summary

The results of the chronic toxicity studies, the ICH battery of genotoxicity studies, and the rodent carcinogenicity studies showed no evidence of an increased risk of carcinogenicity following up to two years repeated TIW dosing of FG-4592.

Conclusion from preclinical studies: preclinical evidence suggest FG-4592 does not present a carcinogenicity risk.

Summaries of all completed, nonclinical studies for roxadustat can be found in the current version of the Investigator's Brochure.

4. OBJECTIVES AND ENDPOINTS

4.1. Objectives

4.1.1. Primary Objective

The primary objective of this study is to evaluate the efficacy of roxadustat in the treatment of anemia in patients undergoing multi-cycle myelosuppressive chemotherapy treatment of cancer.

4.1.2. Secondary Objectives

The secondary objectives of this study are:

- Evaluate the safety of roxadustat in this patient population
- Evaluate the impact of roxadustat on RBC transfusion requirements
- Evaluate the effect of roxadustat on several biological indicators including, but not limited to: erythropoietin, hemoglobin, hematocrit, reticulocytes, hepcidin, serum iron, ferritin, transferrin saturation and total iron binding capacity

4.2. Endpoints

Central lab Hb values will be censored for 4 weeks following a blood/pRBC transfusion during the treatment period for all efficacy analyses.

4.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint is maximum change in hemoglobin in 16 weeks from baseline without RBC transfusion.

4.2.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints of this trial are:

- Mean change in hemoglobin level from baseline to week 16 (without RBC transfusion)
- Change in hemoglobin from baseline through week 8, 12, 16 (without RBC transfusion)
- Proportion of patients who achieved a ≥1 g/dL increase in hemoglobin from baseline through week 16
- Time to achieve a ≥1 g/dL increase in hemoglobin from baseline
- Proportion of patients who achieved a ≥1.5 g/dL increase in hemoglobin from baseline through week 16
- Proportion of patients who achieved a hematopoietic response at any time in the study (defined as an increase in Hb of 1.5 g/dL OR attaining a Hb of 11)
- Proportion of patients who achieved a ≥2 g/dL increase in hemoglobin from baseline through week 16

- Number (%) of patients who had a RBC transfusion from beginning of Week 5 (Day 29) to week 16

4.2.3. Additional Efficacy Endpoints

- Proportion of patients who achieved a ≥1 g/dL increase in hemoglobin from baseline through week 8 and 12
- Proportion of patients who achieved a ≥1.5 g/dL increase in hemoglobin from baseline through week 8 and 12
- Number (%) of patients that require transfusion as medical intervention and/or ESA (erythropoiesis stimulating agent) as a rescue agent. [Time Frame: 16 weeks]
- Percentage of Participants by Tumor Type With Improvement in FACIT-F (fatigue) and Increase in Hemoglobin ≥ 1 g/dL [Time Frame: baseline to week 16]
- Change from Baseline in Quality of life as measured by:

  Functional Assessment of Cancer Therapy-Anemia (FACT-An) test
  [Time Frame: baseline to week 8 and 16]

4.2.4. Exploratory Evaluations

- Effect on hepcidin and iron metabolism
- Effect on cholesterol parameters and lipid metabolism

4.2.5. Subgroup Analyses

- Tumor Type
- Chemotherapy regimen [i.e. platinum vs non-platinum]
- Other clinically relevant characteristics
- Roxadustat PopPK
- Paclitaxel DDI

4.3. Safety Assessments

Safety will be assessed by evaluating the following over the 16-week treatment plus 4-week follow-up periods of the study:

- Adverse Event and Serious Adverse Event Reporting
- Number (%) of patients receiving transfusions
- Various clinical laboratory measurements/values.

5. INVESTIGATIONAL PLAN

5.1. Overall Study Design

This is a Phase 2, open label study. The study will evaluate the efficacy of roxadustat for the treatment of anemia in patients receiving multi-cycle treatments of myelosuppressive chemotherapy. A total of up to 100 patients will be enrolled in this trial, across approximately 10-20 study centers in the United States.

This trial has three study periods:

- Screening (up to 28 days)
- 16-week Treatment with roxadustat
- 4-week Follow-Up

All screening procedures are to be completed within 28 days prior to Study Day 1. Patients will be evaluated per the protocol inclusion/exclusion criteria to determine eligibility for participation in this trial. Protocol assessments will be completed during screening visits in accordance with Schedule of Assessments (SOA) to establish a baseline profile, including; demographics, medical history, clinical status and disease stage for each patient. Eligible patients will be enrolled in the trial and receive roxadustat in an open-label manner. The starting dose for the initial 20 patients will be 2.0 mg/kg, with dose titration to Hb levels every 4 weeks. Starting dose(s) for subsequent patients will be selected by the sponsor, informed by the data available from earlier patients treated in the study.

Upon evaluating the pharmacodynamics (hemoglobin) responses after 4 weeks of therapy with the starting dose of 2.0 mg/kg in initial 20 patients, it has been determined to increase the starting dose for newly enrolled patients by one level i.e. from 2.0 mg/kg to 2.5 mg/kg level to achieve optimal hemoglobin response. The maximum permitted dose will remain the same i.e. 400 mg or 3.5 mg/kg TIW (whichever is lower).

The selected starting dose level of subsequent patients will not exceed the highest dose level received by any individual patient in the study up to that point and will be within the maximum dose allowed in the protocol. Additionally, the sponsor will review clinical efficacy and safety response on an ongoing basis and take into account potential impact of certain baseline patient characteristics or chemotherapy regimens (such as from patients on a platinum vs non-platinum containing regimen) on treatment response in the selection of subsequent patients of such characteristics and starting dose(s) of subsequent patients. This may result in different starting dose revisions for each group. Lastly, if there is more than one starting dose cohort open for enrollment at the same time for a certain subgroup, such as a platinum (or non-platinum) treatment subgroup, patients will be randomized to receive a starting dose. A comprehensive table of potential doses is contained in the protocol body and in Appendix 2. Finally, starting doses will not be adjusted for platinum containing or non-platinum containing regimens until 8 patients in a group have been dosed at a specific dose level.

Patients will undergo 16 weeks of study treatment with roxadustat. Study visits are scheduled every 2 weeks. Patients' clinical status will be regularly evaluated. If disease progression occurs during the treatment period, patients will be discontinued from study treatment and should continue to be followed for safety evaluation throughout the follow-up period.

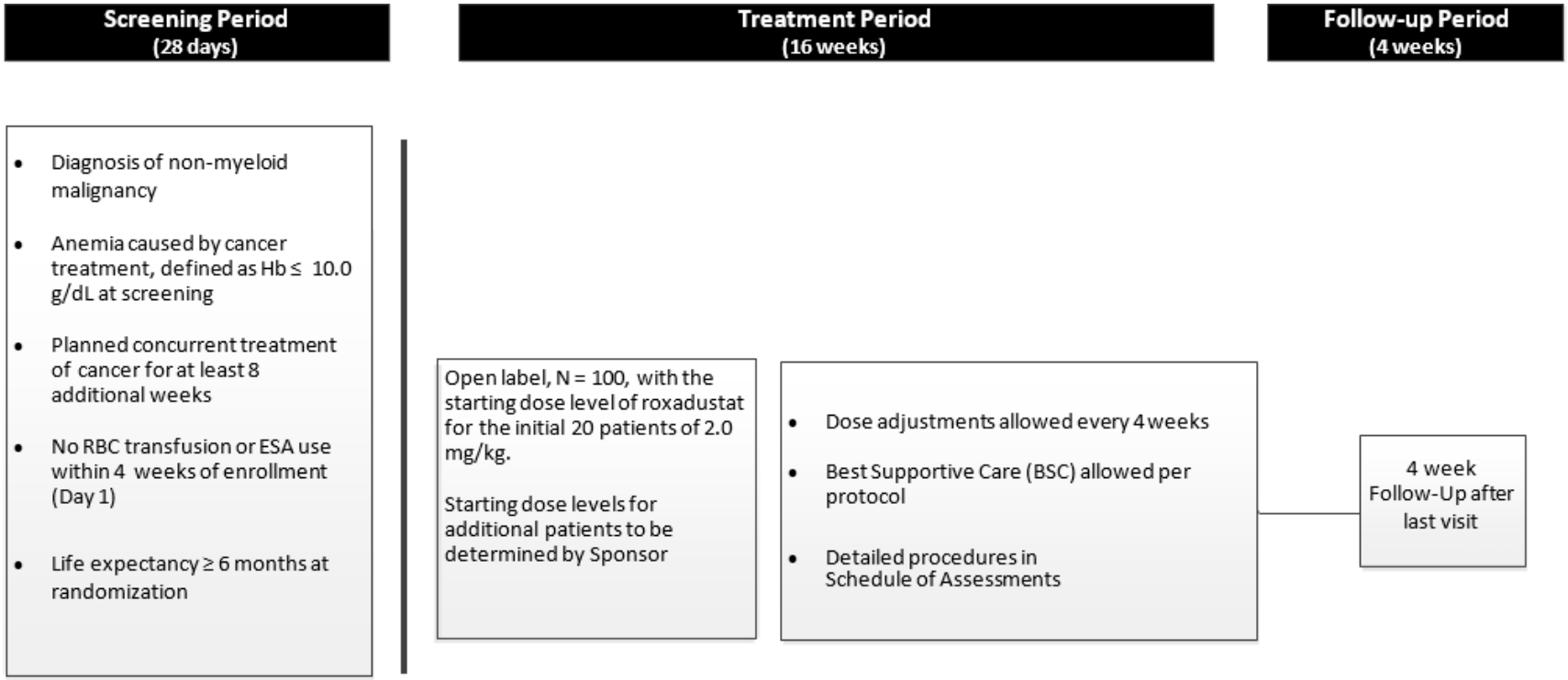
All patients who complete 16 weeks of treatment with study medication will undergo a 4-week follow-up period after the last dose of study medication.

Patients who discontinue study medication early (for any reason whatsoever) will have a 4-week follow-up visit after stopping study medication. See Section 8.0 for details. A schematic overview of the study is provided in Figure 4. Study Schema A detailed overview of assessments and the timing of assessments is provided in Appendix 1

5.1.1. Estimated Study Duration

It is anticipated that enrollment will be complete within 9-12 months from first patient enrolled. All patients will complete up to 16 weeks of study treatment and at least 28 days of safety follow-up. Therefore, it is anticipated that the entire duration of the study will be approximately 1 to 1.5 years from time of first patient enrolled.

Figure 4. Study Schema



5.2. Treatment Assignment

5.2.1. Enrollment

Approximately (up to) 100 patients will be enrolled into this study

No stratification is planned for this study, however sub-groups analyses will be performed as described in the separate statistical analysis plan (SAP). Sub-Groups of interest will include the following:

- Tumor type
- Chemotherapy regimen [i.e. platinum vs non-platinum]
- Other clinically relevant characteristics

Importantly, the initial 8 patients in each of the platinum and non-platinum containing groups will all receive the initial starting dose of 2.0 mg/kg. Data from each group will be examined separately to determine the need of a potential dose step increase for each group. It is possible that one group will have a dose increase and the other group will remain at the initial starting dose level.

5.2.2. Treatment Assignment

All patients will receive roxadustat.

5.3. Blinding

Not applicable to this open-label study.

6. SELECTION AND WITHDRAWAL OF PATIENTS

6.1. Patient Inclusion Criteria

In order to be eligible for inclusion in this trial, a patient must meet all of the following:

1. Diagnosis of non-myeloid malignancy. Current documentation of disease burden (e.g. CT scan) within 3 months prior to enrollment (Day 1)
2. Anemia caused by cancer treatment (myelosuppressive chemotherapy), defined as Hb ≤ 10.0 g/dL at screening
3. Planned concurrent treatment of cancer (myelosuppressive chemotherapy) for at least 8 additional weeks
4. Age ≥18 years
5. Body weight ≥45 kg and < 150 kg
6. ECOG performance status of 0, 1, or 2 at last screen visit
7. Patient must be capable of giving written informed consent
8. Understand and sign informed consent; be willing to comply with all study procedures
9. Estimated life expectancy ≥ 6 months at enrollment (Day 1)

6.2. Patient Exclusion Criteria

Patients will be ineligible for and excluded from this trial if any of the following apply:

1. Patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure
2. Patients who are only receiving hormonal products, biological products, novel immunosuppressive products (such as PD-1 and PD-L1 checkpoint inhibitors) or targeted biological or radiation therapy to treat/manage their cancer. (Patients receiving concomitant myelosuppressive therapy if not intended for cure may be allowed to participate)
3. Patients who prefer a Red Blood Cell (RBC) transfusion as treatment of anemia at time of study entry, over receiving the investigational drug Roxadustat
4. Received an RBC transfusion or ESA within 4 weeks of enrollment (Day 1)
5. Alanine aminotransferase (AST) >3 x upper limit of normal (ULN), OR aspartate aminotransferase (ALT) >3 x ULN, OR total bilirubin (TBL) >1.5 x ULN– will exclude a patient from entering the study (patients with TBL up to 2x ULN may be allowed if ALT/AST are within normal limit and investigator has no safety concerns)
6. Inadequate iron stores as defined as ferritin < 50 ng/mL
7. Any investigational drug within 8-weeks prior to Day 1 Treatment or plans to use any of these medications during the course of clinical trial participation
8. Anticipated use of dapsone during the study

9. Clinically significant anemia due to other etiologies such as iron deficiency, vitamin B12 or folate deficiency, autoimmune or hereditary hemolysis or anemia, hemorrhage, or hereditary anemia such as sickle cell anemia, thalassemia, or MDS
10. Active infection(s) requiring chronic antibiotic therapy
11. Estimated Glomerular Filtration Rate (eGFR) <30 mL/min based on 4-variable MDRD equation
12. Thromboembolic event (deep vein thrombosis (DVT), pulmonary embolism, myocardial infarction, stroke, transient ischemic attack (TIA) within previous 6 months of screening
13. Significant heart disease, including New York Heart Association (NYHA) Class III or IV congestive heart failure, uncontrolled hypertension or hypotension, or significant valvular or endocardial disease that would put the patient at risk for thromboembolism
14. Clinically significant or uncontrolled ongoing inflammatory/autoimmune disease (e.g., rheumatoid arthritis, Crohn's disease, celiac disease, etc.)
15. History of significant liver disease or active liver disease
16. Major surgery planned during the treatment period
17. Known, active or chronic bleeding
18. Known human immunodeficiency virus (HIV), hepatitis B or hepatitis C infection
19. Clinically significant or uncontrolled medical condition that would affect the patient's ability to participate in the study or confound the study's efficacy or safety results
20. History of leukemia (current or historical Chronic Lymphocytic Leukemia may be allowed)
21. Previous recipients of roxadustat or another hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI)
22. Pregnant or breastfeeding females

6.3. Patient Withdrawal Criteria

Patients may withdraw from study treatment at any time.

Reasons for discontinuing the patient from study treatment include the following:

- Progressive Disease
- Adverse Event
- Lost to Follow-Up
- Use of any ESA (Appendix 5) during the study
- Non-compliance with study drug
- Physician decision
- Pregnancy
- Major protocol deviation that substantially affects patient safety or assessment of efficacy endpoints

- Withdrawal of Consent

Discontinued patients should be evaluated in the clinic for EOT visit, followed for safety and continue in the follow-up period.

6.4. Replacement of Study Patients

Patients will not be replaced in this study.

6.5. Study Termination

FibroGen reserves the right to close any investigational site(s) or terminate the study at any time for any reason. Reasons for the closure of the study site or termination of a study by FibroGen may include (but are not limited to):

- Successful completion of the study at the investigational site
- The required number of patients for the study has been recruited
- Failure of the Investigator to comply with the protocol, GCP guidelines or local requirements
- Safety concerns
- Inadequate recruitment of patients by the Investigator

7. TREATMENT OF PATIENTS

7.1. Study Treatment

Roxadustat is administered as an oral tablet, TIW for up to a maximum of 16 weeks overall study treatment period. If dosing delays occur due to AEs or scheduling conflicts, for example, it is acceptable to hold (not give) roxadustat for one single instance not to exceed a 2-week period. Dosing visits should occur in accordance with the SOA outlined in Appendix 1 whenever possible, regardless of delays in chemotherapy dosing. Dosing of roxadustat should continue even if the planned courses of chemotherapy are halted.

Information regarding storage and handling is found in the FG-4592 Investigator's Brochure and the IP Manual.

7.1.1. Roxadustat

The dose, route and schedule for the administration of roxadustat is provided below in Table 1 as well as in Appendix 2.

Table 1: Starting Dose, Route, and Administration

Dose Level Group	Roxadustat dose level (mg/kg)	45 to <70 kg	70 - 100 kg	> 100 kg
1	2.0	100 mg TIW	150 mg TIW	200 mg TIW

Dose adjustment evaluation will be made every 4 weeks, and dose will be titrated to Hb level and rate of Hb change according to Appendix 2. Dose escalation decisions are based on results from LOCAL Hb testing. This can either be hemocue (supplied by FibroGen) or via local lab as long as there is real time turnaround of results to prevent patient inconvenience.

Additional information on dose escalation steps and other potential starting dose levels is given in Appendix 2 as well as the table below.

Table 2. Roxadustat Dose Levels

Body Weight	Dose Levels				
	Approx. 1.0 mg/kg	Approx. 1.5 mg/kg	Approx. 2.0 mg/kg	Approx. 2.5 mg/kg	Approx. 3.0 mg/kg	Approx. 3.5 mg/kg
45 - < 70 kg	50 mg TIW	70 mg TIW	100 mg TIW	150 mg TIW	200 mg TIW*	250 mg TIW*
70-100 kg	100 mg TIW	120 mg TIW	150 mg TIW	200 mg TIW	250 mg TIW	300 mg TIW*
>100 kg	120 mg TIW	150 mg TIW	200 mg TIW	250 mg TIW	300 mg TIW	350 mg TIW

Principal Investigator (PI) and/or treating physician will determine when to transfuse a patient based on clinical judgement.

Evaluation for dose modification/adjustment will occur every 4 weeks. Any potential dose escalation/dose reduction will be at pre-defined dose step increments.

After the initial 20 patients are enrolled, starting dose(s) for additional patients will be selected by the sponsor, informed by the data available from earlier patients treated in the study.

Starting dose for newly enrolled patients:

Upon evaluating the pharmacodynamics (hemoglobin) responses after 4 weeks of therapy with the starting dose of 2.0 mg/kg in initial 20 patients, it has been determined to increase the starting dose for newly enrolled patients by one level i.e. from 2.0 mg/kg to 2.5 mg/kg level to achieve optimal hemoglobin response.

Dose Level Group	Roxadustat Dose Level (mg/kg)	45 to < 70 kg	70 - 100 kg	> 100 kg
1	2.5	150 mg TIW	200 mg TIW	250 mg TIW

The selected starting dose level will not exceed the highest dose level received by any individual patient in the study up to that point and will be within the maximum dose allowed in the protocol. Additionally, the sponsor will review clinical efficacy and safety response on an ongoing basis and take into account potential impact of certain baseline patient characteristics or chemotherapy regimens (such as from patients on a platinum vs non-platinum containing regimen) on treatment response in the selection of patients of baseline characteristics and starting dose(s) of subsequent patients. Lastly, if there is more than one starting dose cohort open for enrollment at the same time for a certain subgroup, such as platinum (or non-platinum) treatment

group, patients will be randomized to receive a starting dose. A comprehensive table of potential doses is contained in the protocol body and in Appendix 2.

7.1.2. Chemotherapy

The dose, route, and schedule for administration of any chemotherapeutic agent will be decided and administered per treating physicians according to standard treatment algorithms.

7.1.3. Dose Administration and Modifications

See Study IP Manual for details regarding dose preparation and administration.

Roxadustat can be given either before or after chemotherapy, but timing should be consistent throughout the course of the study.

In the event that chemotherapy is modified, withheld, or terminated as per standard of care, the dosing schedule of roxadustat should be maintained.

7.1.4. Treatment Compliance

Roxadustat will be dispensed by qualified personnel at the investigational sites; dosing history and study medication reconciliation will be documented in the corresponding case report form (CRF).

7.1.5. Concomitant Medications, Procedures, and Nondrug Therapies

7.1.5.1. Prohibited Concomitant Medications

Use of ESAs (Appendix 5) and Dapsone in any dose amount is prohibited in the course of the study. Androgens and iron-chelating agents (eg, deferoxamine, deferiprone, or deferasirox therapy) are also prohibited in the course of the study. However, other regular supportive care as clinically indicated is permitted during this trial.

7.1.5.2. Chemotherapy Treatments

If Paclitaxel (e.g. Taxol® or Abraxane®) is given as part of a chemotherapy regimen, roxadustat dosing should be held for 24 hours before and after treatment (time 0 = start of infusion) with this drug. Roxadustat dosing frequency may be adjusted, as needed.

7.1.5.3. Other Potential Drug Interactions

Dose adjustments of strong modulators of CYP2C8 (e.g. gemfibrozil, clopidogrel) and UGT enzymes per physician judgment are allowed.

7.1.5.4. Phosphate Binders

When coadministered with roxadustat, in a clinical pharmacology study, the bioavailability of roxadustat was reduced. Patients should be advised to discuss with the Investigator when changing the dose or dosing time of their phosphate binder while taking study medication.

7.1.5.5. Statins

When coadministered with roxadustat, in clinical pharmacological studies, hydroxymethylglutaryl coenzyme A reductase inhibitor (statin) exposure was increased 2- to 3-

fold. Investigators should consider this interaction and local prescribing information when deciding on the appropriate statin dose for individual patients, bearing in mind the impact of ethnicity, other concomitant medications, renal and hepatic function. Goals of lipid lowering treatment should be maintained as clinically indicated. The dose of statins should not exceed the recommended daily dose in Table 3 below.

Table 3. Recommended Maximum Daily Dose of Statins

Statins	Recommended Maximum Dose (mg/day)
Atorvastatin	40
Simvastatin	5
Rosuvastatin	5
Pravastatin	40
Fluvastatin	20
Pitavastatin	2
Lovastatin	20

7.1.5.6. Supplemental Iron Use

Oral iron supplementation is allowed. IV iron use is prohibited, but may be considered if patient is iron-deficient and unresponsive to oral iron supplementation and lacking erythroid response to study medication. This would require discussion with the Medical Monitor.

7.1.5.7. Contraception Requirements

Female patients of childbearing potential are required to use double barrier contraception methods during the entire conduct of the study and for 3 months after the last dose of study drug. Male subjects with female partners of childbearing potential who are not using birth control as described above must use a barrier method of contraception (e.g., condom) if not surgically sterile (i.e., vasectomy).

For patients discontinuing study medication prematurely, it is recommended that they continue to practice contraceptive methods for 12 weeks following the last dose of study treatment.

Pregnancy, spontaneous or therapeutic abortion, or events related to pregnancy must be reported.

7.2. Study Drug Materials and Management

Additional details regarding study drug material and management can be found in the Study Investigational Product (IP) Manual.

7.2.1. FibroGen Investigational Product (Roxadustat)

Roxadustat is supplied by FibroGen as red-coated, oval tablets for oral administration, in strengths of 20 mg, 50 mg, 100 mg, and 150 mg. The excipients include lactose monohydrate, microcrystalline cellulose, povidone, croscarmellose sodium, magnesium stearate, and colorant Red Opadry II. All ingredients used for manufacture of roxadustat comply with US and European Union compendia or regulatory standards. Strengths are different in size and debossing reflects the strength (i.e., 20, 50, 100 and 150 mg).

7.2.2. Study Drug Packaging and Labeling

Labels will be prepared and will comply with Good Manufacturing Practice and local regulatory guidelines.

7.2.3. Study Drug Storage

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

7.2.4. Study Drug Administration

All patients will take doses TIW for the entire duration of the study unless frequency adjustment is needed for concomitant Paclitaxel use. Roxadustat will be dispensed to patients with instructions for self-administration of the tablets orally on each dosing day, according to the dosing schedule. The tablets are to be swallowed whole. Tablets should not be cut.

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

7.2.5. Overdose, Emergency Procedures, and Management of Overdose

The maximum tolerated dose of roxadustat has not been established in humans. For the purpose of this study, the maximum allowed roxadustat dose is set at 400 mg or 3.5 mg/kg/dose, whichever is lower. Any dosing of study medication in this study exceeding the maximum allowed roxadustat dose should be reported within 24 hours. The Medical Monitor should be contacted as soon as possible. Symptoms associated with overdosing, if any, will be reported as adverse events.

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

7.2.6. Study Drug Handling and Disposal

All study drug provided by the Sponsor should be retained at the site until otherwise instructed in writing by the Sponsor (or designee). The Sponsor (or designee) will perform drug accountability and reconciliation for all study drug received at the site prior to approving study drug return/destruction. Upon completion of accountability/reconciliation or upon completion of the study or termination of the investigational site, all used, unused, partially used study drug, and all study drug that was not dispensed will be shipped to a destruction site designated by the Sponsor (or designee) for destruction. Study drug may be destroyed on site according to local/institutional policies by the pharmacy/authorized staff with approval from Sponsor (or designee). Please refer to the IP Manual for additional information on study drug accountability.

8. ASSESSMENTS OF EFFICACY

8.1. Study Assessments

A signed and dated IRB/IEC-approved informed consent must be obtained before any study-specific assessments are performed. Assessments that are part of routine care are not considered study-specific and may be used at screening to determine eligibility. All patients will be screened for eligibility before enrollment. Only eligible patients will enrolled into the study.

8.1.1. Screening Period

All screening procedures must be performed within 28 days of Day 1. Study procedures to be performed during the screening period can be found in the Schedule of Assessments (Appendix 1). Central laboratory results will be used to determine eligibility. No IWRS system will be utilized for this study. All enrolled patients will be entered in the clinical database (EDC).

Current disease burden measurement at baseline is required to be done within 3 months of enrollment (Day 1), documented in CRF, and the scans or other reports (used for disease burden documentation), as applicable, be available for comparison if needed:

1. For tumor lesion(s) which are measurable by RECIST criteria, relevant imaging stud(ies) of choice to be determined by PI, i.e. CT, MRI, ultrasound, etc, is/are required.
2. For bone lesion (not measurable by RECIST), a bone scan is required.

8.1.2. 16-Week Treatment Period

All enrolled patients will have clinic visits at a scheduled frequency of every 2 weeks throughout the 16-week period. Assessments will be done as outlined in the Schedule of Assessments in Appendix 1.

8.1.3. Follow-up Period

All patients enrolled will have a safety follow-up visit approximately 28 days after the last dose of study treatment. After the protocol-required reporting period (28 days after the last dose), the investigator does not need to actively monitor patients for serious adverse events (SAEs). However, if the investigator becomes aware of a SAE that may be possibly related to study treatment after the protocol-required reporting period, the investigator may report the event to FibroGen as outlined in Section 9.0. SAEs reported outside of the protocol-required reporting period will be captured within the safety database only as clinical trial cases for the purposes of expedited reporting.

8.1.4. Missed Visits

Study treatment may be withheld/interrupted due to safety reasons, resulting in a “missed” visit. These visits may be rescheduled to accommodate interruptions within a total window of + 4 weeks over the course of the study. Adjustments to the dosing schedule for roxadustat should be discussed with the study Medical Monitor. If a visit is missed and not rescheduled, it will be captured accordingly in the clinical database.

8.1.5. Unscheduled Visits

Unscheduled visits/assessments may be required at the discretion of the Investigator. Unscheduled visit data will be captured accordingly in the clinical database.

8.1.6. Early Withdrawal from Treatment

Patients who prematurely discontinue the study should be strongly encouraged to complete the final evaluations scheduled for the EOT visit as specific in the SOA (Appendix 1). These patients must be followed for safety for 28 days following their last dose of study drug. Discontinued patients will continue in the Follow-up period and be followed for progression, survival and additional anti-cancer therapies.

8.2. Assessments

Refer to the Schedule of Assessments (Appendix 1) for details regarding the timing and frequency of study assessments.

8.2.1. Vital Signs (Including Weight and Height)

Vital signs to be collected include; heart rate, blood pressure, respirations and temperature:

- Heart rate should be collected as beats/min
- Systolic and diastolic blood pressure should be collected from patients in seated position
- Respirations should be collected as breaths/min
- Temperature should be taken as oral or tympanic and captured as °F or °C

Weight is collected during screening and Day 1. Dosing is based at patient's weight at Day 1 of treatment. Height is collected during screening only.

8.2.2. Physical Exam

A full physical exam is required during screening, EOT and at the Follow-Up visit. A full physical exam may include, but is not limited to, review of the following systems:

- General Appearance, HEENT, Lungs, Heart, Chest & Back, Abdomen, Extremities, Neurologic, Skin

8.2.3. Electrocardiogram (ECG or EKG)

EKGs will be performed in accordance with institutional standards at Week 1/Day 1 prior to randomization, EOT and 4-week Follow-up.

8.2.4. Laboratory Evaluations

Details regarding sample collection, preparation and transport can be found in the central lab manual. Importantly, dose adjustments/escalations will be made based on results from LOCAL Hb testing. This can either be hemocue (supplied by FibroGen) or via local lab as long as there is real time turnaround of results to prevent patient inconvenience. However, if in PI's opinion, the local lab value does not accurately reflect patient's current condition, PI may delay adjustment until central lab result is available.

A set of serum and plasma samples may be drawn and stored for 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 for the diagnosis of genetic disorders on these samples.

8.2.4.1. Central Laboratory Evaluations

The following labs will be evaluated by a central laboratory in accordance with the SOA (Appendix 1):

Table 4. Laboratory Tests

CBC:	**Chemistry Panel:**
Absolute neutrophil count (ANC)	Bicarbonate
Eosinophils	BUN
Erythrocyte count (RBC)	Calcium
Hematocrit	Creatinine
INR	Chloride
PTT/PT	Magnesium
Hemoglobin	Glucose
Leukocyte count (WBC)	ALP
Lymphocytes	ALT
Mean corpuscular volume	AST
Monocytes	Bilirubin, total
Neutrophils	Albumin
Platelets	Phosphorous
CRP	Potassium
Other:	Sodium
Hepcidin	

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; CRP = C-reactive protein; INR = international normalized ratio, PT/PTT = prothrombin time/partial thromboplastin time; RBC = red blood cell; WBC = white blood cell.

Central lab results obtained during the screening period will be used to determine patient eligibility for participation in the trial. Central lab results will be reviewed by the investigator for clinical significance and to determine appropriate reporting of adverse events (see Section 9.3.7).

Local labs results may be used to evaluate patient condition prior to dosing. Local lab results will not be captured in the clinical database except for local Hb testing. These local Hb values will be recorded in the CRF and used for dose adjustment assessments only. Clinically significant local lab findings during the study, if any, should be confirmed via central lab. If situation permits, a sample should be sent to the central lab at the same time for study record.

8.2.4.2. Pharmacokinetics and Pharmacodynamics

Roxadustat Population PK sub-study:

There will be a population PK sub-study for roxadustat in this protocol. Sites will not be required to participate in the pharmacokinetic/pharmacodynamics (PK/PD) portion of the study. Patients at sites that have been qualified to participate in the PK/PD portion of the study will sign an additional informed consent form if they wish to participate in the PK/PD sub-study. Patients are NOT required to participate in the sub-study, and this decision will NOT make them ineligible for the overall study protocol. Samples will be taken after 4 weeks of treatment at each dose level at 1 or 2 pre-dose sample times and at 1-4 hours post-dose (ideally on the same day as the pre-dose sample but not required). In addition, two samples should be taken at > 5 hours after dosing (may be at different clinic visits consequent with other assessments). Accuracy of time of most recent dosing and sampling is important to capture.

Paclitaxel PK sub-study:

There will be a PK sub-study to evaluate the effect of roxadustat timing of administration on the pharmacokinetics of paclitaxel in this protocol. Patients are NOT required to participate in the sub-study, and this decision will NOT make them ineligible for the overall study protocol. Sites will not be required to participate in the pharmacokinetic sub-study. Patients at sites that have been qualified to participate in the PK portion of the study will sign an informed consent if they wish to participate in the sub-study.

Additional details are provided in Appendix 6 for PK sub-study to investigate the potential effect of Roxadustat on the pharmacokinetics of paclitaxel.

8.2.4.3. Eastern Cooperative Oncology Group (ECOG)

These scales and criteria are used by doctors and researchers to assess how a patient's disease is progressing, to assess how the disease affects the daily living abilities of the patient, and to determine appropriate treatment and prognosis (Oken, 1982). The ECOG performance scale will be used to evaluate patient's performance status during screening and throughout the trial. See Appendix 3.

8.2.5. Patient Reported Outcomes (PROs)

Patient reported outcome (PRO) data will be collected in all patients to evaluate the most important patient reported symptoms, treatment related symptoms and functional impacts that may be responsive to treatment. FACIT-F (fatigue) and FACT-An (anemia) questionnaires will be administered as specified in the SOA (see Appendix 1). All questionnaires should be completed by patients PRIOR to any procedures/treatments performed on that study day.

8.2.5.1. FACIT-F

FACIT-F, a subset of FACT-An, is a health related quality of life questionnaire (HRQOL) assessing fatigue and anemia-related concerns in people with chronic illness including cancer. The most current validated version of this questionnaire will be used for this study. This questionnaire will be collected at baseline (Day 1), and at various times as described in the SOA.

8.2.5.2. FACT-An

FACT-An is a HRQOL instrument that specifically addresses symptoms of anemia related to cancer- therapy and has been validated in diverse cancer populations. This questionnaire will be collected at baseline (Day 1), and at various times as described in the SOA.

9. ASSESSMENTS OF SAFETY

9.1. Background

Adverse event reports from investigators are the critical building blocks to the development of the safety profile of the Study Drug. Patients will be asked non-leading questions in general terms to determine the occurrence of AEs, according to the schedule outlined in Appendix 1. 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 or designated safety management vendor all SAEs, regardless of whether the investigator believes they are related to the study drug.

9.2. Definitions

9.2.1. Definition of an Adverse Event (AE)

An adverse event is defined as any untoward medical occurrence in a clinical trial patient. The event does not necessarily have a causal relationship with study treatment. The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the patient as defined in the study protocol are recorded in the patient's medical record. The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition (e.g., diabetes, migraine headaches and gout) has increased in severity, frequency, and/or duration, and/or has an association with a significantly worse outcome. A pre-existing condition that has not worsened during the study or involves an intervention such as elective cosmetic surgery or a medical procedure while on study, is not considered an adverse event. (Section 9.3.1).

9.2.2. Definition of a Serious Adverse Event (SAE)

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

- Death,
- A life-threatening AE (i.e., if in the view of the investigator or sponsor, the patient 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
- Is considered a medically important event not meeting the above criteria, but which may jeopardize a patient or may require medical or surgical intervention to prevent one of the other criteria listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, and blood dyscrasias or convulsions that do not result in inpatient hospitalization.

Please note that death is an outcome, not an event; the primary cause of death would be the adverse event.

Surgical procedures, per se, are not SAEs. The condition requiring the surgical procedure, however, may be an SAE.

Scheduled or pre-planned hospitalization or prolongation of a hospitalization due to standard of care assessments and procedures (including elective procedures) do not warrant reporting as adverse events unless resulting observations are deemed by the Investigator to meet the definition of an adverse event.

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

9.3.1. Adverse Event Reporting Period

The safety reporting period begins after the patient has signed the informed consent and ends 28 days after the last dose of study drug. It is only required that SAEs be reported prior to first dose, while all AEs (serious and non-serious) be reported thereafter. The investigator should notify FibroGen of any death or other SAEs occurring after a patient has discontinued or terminated study participation that may reasonably be related to this study (Section 9.3.5). Pregnancy reporting requirements are outlined in Section 9.3.6.

Adverse events will be followed until resolved, stable, or until the patient's last study visit or patient is lost to follow-up.

9.3.2. Adverse Event Eliciting/Reporting

During the AE reporting period, study site personnel will query each patient 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 patient's well-being and any possible changes from the BL or previous visit, but shall not be specifically solicited. There will be no directed questioning for any specific AE. This does not preclude the site from collecting and recording any AEs reported by the patient 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. The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study patient represents a clinically significant change from the patient's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event. The investigator is expected to follow reported adverse events until stabilization or reversibility.

The following attributes must be assigned to each AE:

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

9.3.3. Assessing Adverse Event Severity

AEs, including abnormal clinical laboratory values, should be graded using the National Cancer Institute (NCI) Common Terminology Criteria for AE (CTCAE) v 4.0 guidelines. For terms not specified as part of NCI CTCAE, the following guidelines should be used to determine grade:

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

- **Grade 1, Mild:** Asymptomatic or mild symptoms which the patient finds easily tolerated. The event is of little concern to the patient and/or of little-or-no clinical significance; intervention not indicated.
- **Grade 2, Moderate:** The patient has enough discomfort to cause interference with or change in some of their age-appropriate instrumental activities of daily living (e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money); local or noninvasive intervention indicated.
- **Grade 3, Severe:** The patient is incapacitated and unable to work or participate in many or all usual activities. The event is of definite concern to the patient and/or poses substantial risk to the patient'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 patient was at immediate risk of death from the event as it occurred.
- **Grade 5, Death**: Fatal AE.

9.3.4. 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 trials; therefore, AE reports from investigators are critically important. The assessment of whether an AE is causally related to the study drug(s) using an evidence-based approach is critical in order to appropriately describe the safety profile study drug(s). Default reporting of individual events as possibly related is uninformative and does not meaningfully contribute to the development of the study drug's safety profile.

The investigator must provide an evidence-based 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 sufficient evidence to assess an event as related to study drug.

- Related:
  - Any event for which there is sufficient evidence to suggest that the study drug may have caused the event. For example, an unanticipated medical condition occurs which resolves with study drug interruption and re- occurs with re-administration of study drug; another example is a typical drug-related medical condition such as a rash that occurred shortly after first dose of study drug.
- Not Related:
  - The event represents a pre-existing underlying disease that has not worsened on study
  - The event has the same characteristics of a known side-effect associated with a co-medication
  - The event is an anticipated medical condition of anticipated severity for the study population
  - The most plausible explanation for the event is a factor that is independent of exposure to study drug

9.3.5. Reporting Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the patient that occur after signing of the informed consent/assent through 28 days after the last dose of roxadustat are recorded in the patient's medical record and are submitted to FibroGen. All SAEs must be submitted to FibroGen within 24 hours following the investigator's knowledge of the event via the SAE report form.

If a patient is permanently withdrawn from protocol required therapies because of a serious adverse event, this information must be submitted to FibroGen. FibroGen will report serious adverse events and/or suspected unexpected serious adverse reactions as required to regulatory authorities, investigators/institutions, and central IRBs/IECs in compliance with all reporting requirements according to local regulations and Good Clinical Practice (GCP).

There is no requirement to monitor study patients for serious adverse events following the protocol-required reporting period or after end of study. However, these serious adverse events can be reported to FibroGen. In some countries (e.g. European Union [EU] member states), investigators are required to report serious adverse events that they become aware of after end of study. If serious adverse events are reported, the investigator is to report them to FibroGen within 24 hours following the investigator's knowledge of the event. Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases for the purposes of expedited reporting; these cases will not be included in the clinical study report.

To report an SAE, the investigator must complete an SAE Report Form and fax or email the completed form to the Sponsor or its designated safety management vendor.

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

- Patient number, sex and age
- The date of report
- A description of the SAE (event, seriousness of the event)
- Causal relationship to the study drug
- Follow-up information for the event should be sent promptly.

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

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

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

9.3.5.2. Deaths

The investigator will report the fatal event to the Sponsor's medical monitor. The investigator must provide a causal assessment of the relationship of the event to the study drug according to the guidance in Section 9.3.5.

If the death occurred within the AE collection and reporting period (signed ICF to 4 weeks after last dose) and meets the reporting criteria, the investigator must submit the SAE Report Form in the same manner as described above in Section 9.3.5. If the investigator becomes aware of a death occurring after the AE reporting period and considers it related to roxadustat, it will be reported as an SAE.

9.3.6. Pregnancies: Reporting and Follow-up of Patients

The outcome of all pregnancies for female patients should be followed up and documented as described. A Pregnancy Report Form must be completed and submitted to Sponsor or designated safety management vendor within 24 hours of the investigator becoming aware of the pregnancy. The investigator must follow-up to completion of the pregnancy to ascertain its outcome (e.g. spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) and whether any AEs occur during the pregnancy or birth. The outcome of the pregnancy must be reported by the investigator on a Pregnancy Outcome Report Form, which should be sent to the Sponsor and/or its designated safety vendor within 24 hours of the investigator becoming aware of the outcome.

Pregnancy itself is not an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Pregnancies are followed up to outcome even if the patient was discontinued from the study. Congenital

abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

Pregnancy of the patient's partners is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should if possible be followed up and documented as described. To capture information about a pregnancy from the partner of a male patient, the male patient's partner consent must be obtained to collect information related to the pregnancy and outcome (should be handled on a case by case basis with IRB/IEC approval); the male patient should not be asked to provide this information.

If a lactation case occurs while the female patient is taking protocol-required therapies, report the lactation case to FibroGen. In addition to reporting a lactation case during the study, investigators should monitor for lactation cases that occur after the last dose of protocol-required therapies through 3 months after the last dose of roxadustat. Any lactation case should be reported to FibroGen's Safety within 24 hours of the investigator's knowledge of event.

9.3.7. Abnormal Laboratory Findings

An abnormal laboratory finding in absence of any other signs or symptoms is not necessarily an AE. The investigator must review and assess all results provided by the central laboratory throughout the study in a timely manner, and determine whether any abnormal laboratory values are clinically significant (CS) or not clinically significant (NCS), and whether there are associated signs and symptoms. Laboratory abnormalities should be considered clinically significant when they occur after taking study medication, reflect a meaningful change from the screening value(s), and require active management (e.g., abnormalities that require study treatment dose modification, discontinuation, more frequent follow-up assessments, etc.).

Clinically significant laboratory abnormalities will be reported as AEs. If the abnormal laboratory finding is accompanied by signs or symptoms, report the signs and symptoms as the AE in lieu of the abnormal laboratory value. If a diagnosis is available, report the diagnosis.

9.3.8. Safety Monitoring

9.3.8.1. Data Monitoring Committee (DMC)

No data monitoring committee will be established for this open label Phase 2 study.

10. STATISTICS

10.1. Sample Size Determination

Up to approximately 100 patients will be enrolled into this study. The sample size is determined by clinical judgment, not by statistical power analysis.

10.2. Analysis Populations

10.2.1. All Enrolled or Intent-to-Treat (ITT) Population

Defined as all patients enrolled in the roxadustat treatment period, regardless of whether patients received any study drug.

10.2.2. Full Analysis Set (FAS) Population

Defined as all enrolled patients who receive at least one dose of roxadustat, have a baseline Hb and at least one corresponding on-treatment Hb assessment. The FAS population will be used for efficacy analyses.

10.2.3. Efficacy Evaluable (EE) Population

Defined as all enrolled patients who receive roxadustat for at least 4 weeks, and have at least one Hb value after 4 weeks or longer, obtained within 2 weeks of last dose.

The EE population will be primarily used for efficacy analyses.

10.2.4. Safety (SAF) Population

Defined as all patients who took at least one dose of study medication. The primary analysis of safety will be based on the Safety population.

10.3. Statistical Analysis

10.3.1. General Considerations

Summary statistics will consist of number of patients (N), means, standard deviations, medians, and minimum and maximum values for continuous variables, and counts and percentages for categorical variables. For efficacy endpoints, the standard error and 95% confidence intervals will be added as part of the descriptive summaries. Tables will summarize all efficacy and safety measures by time point, if appropriate. All analyses will be based on available data unless otherwise specified.

10.3.2. Patient Enrollment and Disposition

Patient enrollment and disposition will be presented for all enrolled patients. The total number and percent of patients who completed or discontinued, and reasons for early discontinuation, will be summarized.

10.3.3. Demographics and Baseline Characteristics

Demographics (age, race, sex), baseline characteristics (e.g., height, weight), and patient disease characteristics will be summarized for the ITT population and safety population.

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

10.3.4. Efficacy Analyses

10.3.4.1. Analysis of the Primary Endpoint

Hemoglobin results obtained from the central laboratory will be used for all efficacy analyses. Baseline Hb is defined as the mean of the central laboratory Hb values prior to the first dose of study drug.

The primary efficacy analysis will be based on the EE and FAS population using an observed case dataset. The primary efficacy parameter, defined as maximum change in hemoglobin from baseline in 16 weeks without RBC transfusion, will be summarized by using descriptive statistics. Hb values within 4 weeks after a RBC transfusion will be censored.

The mean change from baseline hemoglobin (without a RBC transfusion) will be summarized using descriptive statistics by visit. Maximum change from baseline will also be analyzed using Analysis of covariance using Cancer types as a class variable and the baseline Hb as a covariate. Least Square Means will be calculated from the model and tested against 0 for each cancer type and overall.

In addition, missing hemoglobin data, either because of a missed visit or collected within 4 weeks after a RBC transfusion will be imputed in the last-observation-carried-forward (LOCF) approach.

Number (%) of patients meeting specific criteria specified in the protocol as secondary efficacy endpoints will also be summarized descriptively and the Clopper – Pearson confidence limits approach will be used.

The percentages of patients who have a hematopoietic response, who receive at least one RBC transfusion will also be summarized descriptively and estimated using the Kaplan–Meier (KM) method.

10.3.4.2. Analysis of the Secondary and Additional Endpoints

The mean change from baseline hemoglobin (without a RBC transfusion) will be summarized using descriptive statistics by visit. This will also be analyzed similar to the model used for the primary endpoint.

Additional efficacy analyses will use the EE and FAS populations. Number (%) of patients require transfusion/ESA will be summarized descriptively. Change from baseline in quality of life composite scores (as well as selected subscale scores, if applicable) will be summarized descriptively.

10.3.5. Exploratory Analyses

Changes from baseline in iron parameters, lipid parameters, hepcidin levels, cholesterol parameters and biomarkers will be summarized descriptively.

Subgroup analyses of primary and secondary endpoints will be performed.

10.3.6. Safety Analyses

All patients who received any dose of study drug will be included in the safety analyses.

All safety assessment data, including laboratory assessments (with special emphasis on Hb response and LFTs), vital signs, ECGs, AEs, concomitant medications and therapies will be summarized by time point of collection as appropriate.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA). A treatment emergent adverse event (TEAE) is defined as any new or worsening of an existing condition occurred after the first dose of the study medication and within 28 days after the last dose of study medication. TEAEs will be tabulated to examine their frequency, severity, organ systems affected and relationship to study treatment. Deaths, SAEs, AEs leading to study or treatment discontinuation will be listed or tabulated separately.

Laboratory tests, vital sign measurements, ECG parameters, as well as the changes from baseline will be summarized descriptively by assessment time point. Clinically significant changes from baseline in these safety parameters will be identified. Shift tables will summarize changes for selected laboratory measures.

Medications used prior to and during the study will be coded using The World Health Organization Drug Dictionary (WHODrug). Prior and concomitant medications will be tabulated by therapeutic class and generic name.

10.4. Interim Analysis

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

10.5. Statistical Analysis Plan

A detailed Statistical Analysis Plan (SAP) will be finalized prior to data analysis. The Statistical Analysis Plan (SAP) will include detailed analysis methods, statistical models, definitions, as well as data handling rules. The SAP will document additional exploratory endpoints that are not specified in the protocol. Any significant changes to the analyses described in this protocol will be highlighted in the SAP. Deviations in analyses from the SAP will be detailed in the Clinical Study Report.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1. Data Quality Assurance

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

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

The purpose of trial monitoring is to verify the following:

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

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

11.2. Audit and Inspection

Authorized representatives of the sponsor, a regulatory authority, and/or an IRB/IEC may visit the investigator site to perform audits or inspections, including source data verification and source documentation review. The Investigator will allow the sponsor auditor (or designee), regulatory authority or ethics committee representative to inspect the drug storage area, study drug stocks, drug accountability records, patient charts (e.g. medical records) 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, ICH GCP guidelines, and any applicable regulatory requirements.

The investigator must contact the sponsor, or its third party representative (CRO), immediately if notified by a regulatory authority of an inspection pertaining to this study.

12. ETHICS

12.1. Ethical Considerations

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

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

This protocol, the Informed Consent Form, the Investigator's Brochure, and any information to be given to the patient 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 patient recruitment materials must be approved by the IRB/IEC before the material is used for patient recruitment.

The investigator is responsible for obtaining re-approval by the IRB/IEC annually or as required by the policies and procedures established by the IRB/IEC. Copies of the investigator's annual report and other required reports submitted to the IRB/IEC and copies of the IRB/IEC continuance of approval must be furnished to FibroGen or designee. A copy of the signed FDA Form 1572 or other qualified investigator statement (as required) must also accompany the above approval letter provided to FibroGen.

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

Investigators must maintain a list of appropriate qualified persons to whom the investigator has delegated significant trial-related duties and update the list as staff and their delegated responsibilities change.

12.3. Patient Information and Consent

Prior to participation in any study-specific procedures, the patient must sign (note: all references to "patient" in this section refers to the study patient or his/her legally acceptable representative) an IRB/IEC-approved written Informed Consent Form in his/her native language. The approved written informed consent must adhere to all applicable laws in regards to the safety and confidentiality of the patients. To obtain and document informed consent, the Investigator should comply with applicable regulations, and adhere to ICH GCP standards and the ethical principles in the Declaration of Helsinki (October 2008).

The language in the written information about the study should be as non-technical as practical and should be understandable to the patient. Before informed consent is obtained, the Investigator should provide the patient ample time and opportunity to inquire about the study and to decide whether or not to participate.

All questions about the study should be answered to the satisfaction of the patient. The written Informed Consent Form should be signed and personally dated by the patient and the person who

conducted the informed consent discussion, with any additional signatures obtained as required by applicable local regulations and IRB/IEC requirements. Each patient will be informed that participation is voluntary and that he/she can withdraw from the study at any time. All patients will receive a copy of the signed and dated Informed Consent Form.

If there are any changes to the IRB/IEC approved ICF during the patients' participation in the study, the revised ICF must receive the IRB/IEC's written approval before use and patients must be re-consented to the revised version of the ICF.

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

12.4. Patient Confidentiality

The confidentiality of records that could identify patients should be protected, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements.

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

The processing of personal data in pursuit of this study will be limited to those data that are reasonably necessary to investigate the utility of the study medications used in this study. These data will be processed with adequate precautions to ensure confidentiality according to local laws.

FibroGen ensures that the personal data are:

- collected for a specified and legitimate purpose
- processed fairly and lawfully
- accurate and up to date

Explicit consent for the processing of personal data will be obtained prospectively from the participating patient. FibroGen and/or designees whose responsibilities require access to personal data agree to keep the identity of study patients confidential. This confidentiality will be maintained throughout the complete data processing.

Study patients will be entitled to request confirmation of the existence of personal data held by FibroGen and will have the right to rectify erroneous or inaccurate data prior to database lock.

13. DATA HANDLING AND RECORD KEEPING

13.1. Source Documents

Source documents are original documents, data, and records necessary for the reconstruction and evaluation of the clinical study. The investigator or designee will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each patient enrolled in this clinical study. Source documents must be adequate to reconstruct all data transcribed onto the CRFs and resolved queries.

13.2. Direct Access to Source Documents

The investigator must provide direct access to source data and source documents for trial-related monitoring, audits, IRB/IEC review, and regulatory authority inspection. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the patient to permit such individuals to have access to his/her study-related records, including personal information and medical records.

13.3. Data Collection, Handling, and Verification

All required data will either be entered onto CRFs 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.

All patient 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 (e.g., MedDRA and World Health Organization Drug [WHODrug]) Dictionary.

The investigator is responsible for reviewing, verifying, and approving all patient data (i.e. CRFs and queries) throughout the duration of the study and prior to study completion, ensuring that all data are verifiable with source documents.

13.4. Protocol Deviations

Unless there is a safety concern, there should be no deviations or violations of the study protocol. In the event of a safety concern, the Investigator or designee must document and explain the reason for any deviation from the approved protocol. The Investigator may implement a deviation from, or a change to, the protocol to eliminate an immediate hazard to study participants without prior IRB/IEC approval. Immediately after the implemented deviation or change, the Investigator must submit a report explaining the reasons for the protocol violation or deviation to the IRB/IEC, FibroGen, and to the regulatory authorities, if required.

13.5. Retention of Data

A FibroGen representative will inform the Investigator in writing when it is acceptable to dispose of any study records. To enable evaluation and/or audits from regulatory authorities or FibroGen or designee, the Investigator agrees to keep records, including the identity of all participating

patients (eg, patient identification code list and all source documents), all original signed ICFs, copies of all CRFs, original laboratory reports, detailed records of drug disposition and all essential documents for the conduct of a clinical study. To comply with international regulations, the records should be retained by the Investigator for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, the Investigator may need to retain these documents for a longer period if required by the applicable regulatory requirements or by an agreement with FibroGen.

13.6. Financial Disclosure

The Investigator's disclosable financial interests must be obtained prior to initiation of the study site, at completion of the study at the investigational site, and 1 year following study completion.

The Investigator should promptly update this information if any relevant changes occur during the above described period.

Disclosable financial interests will be recorded on the Investigator Financial Disclosure Form.

Any Investigator(s) added as investigational staff to the form FDA 1572 must complete the Investigator Financial Disclosure Form at the beginning of his/her participation in the study. The Investigator Financial Disclosure Form for any Investigator(s) leaving the clinical site prior to study completion will be obtained prior to study completion.

14. PUBLICATION POLICY

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

15. REFERENCES

Flaharty KK, Caro J, Erslev A, et al. (1990) Pharmacokinetics and erythropoietic response to human recombinant erythropoietin in healthy men. Clin Pharmacol Ther **47:** (5):557-564

Goldberg MA, Schneider TJ, Khan S, Petersen JR (1993) Clinical validation of an RIA for natural and recombinant erythropoietin in serum and plasma. Clin Biochem **26:** (3):183-189

Kato, A., Hishida A, Kumagai H, Furuya R, et al. (1994) Erythropoietin production in patients with chronic renal failure. Ren Fail **16**: (5): 645-651

Maeda H, Hitomi Y, Hirata R, et al. (1992) The effect of phlebotomy on serum erythropoietin levels in normal healthy subjects. Int J Hematol **55:** (2):111-115

Milledge JS, Cotes PM (1985) Serum erythropoietin in humans at high altitude and its relation to plasma renin. J Appl Physiol **59:** (2):360-364

Oken, et.al. Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982

Seely, et.al. Hypoxia (2017) 5:1-9

Semenza GL (2000) HIF-1: mediator of physiological and pathophysiological responses to hypoxia. J Appl Physiol **88:** (4):1474-1480

APPENDICES

Appendix 1. Schedule of Assessments

Procedures	Screening		Treatment Weeks															Follow-up
	28 days			±3 days[1]														±7 days
	S1	S2	Week 1 Day 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16 **EOT[15]**	WK4
Informed consent signature	x																		
Eligibility Review			x																
Med History/Demographics	x																		
Physical Exam	x																	x	x
Weight, height	x		x																x
HbsAg,anti-HCV AB, HIV	x																		
B12, Folate	x																		
ECG[2]			x															x	x
Vital signs[3]	x		x				x				x				x			x	x
ECOG Score[4]	x		x								x							x	
Serum Lipid Panel			x								x							x	x
LFTs[5]	x		x				x				x				x			x	x
Serum chemistry[6]	x		x				x				x				x			x	x
PT, PTT, INR			x															x	x
Hepcidin			x				x				x				x			x	x
Serum hCG pregnancy test[7]	x																		
C-reactive protein			x															x	
CBC[8]	x	x	x		x		x		x		x		x		x			x	x
Local Hemoglobin			x				x				x				x				
Reticulocyte count; CHr			x				x				x				x			x	x
Iron Biomarkers[9]	x		x								x							x	x
Exploratory biomarkers[10]	x										x							x	x
HRQoL Questionnaires[11]			x				x				x				x			x	
Study drug dosing[12]			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Study drug dispensation			x				x				x				x				
Dose adjustment review[13]							x				x				x				
AEs/Con Meds/Procedures	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
PK sub-study[14]							x				x				x			x	

Footnotes:

1. Windows for procedures listed are +/- 3days unless otherwise stated.
2. ECG: no clinically significant findings per PI review at screen period.
3. Vital signs include BP, HR, RR, temperature. If possible, use the same device for BP measurement over the course of the study. Weight at registration/Day 1 will be used for determination of starting dose.
4. ECOG score: must be 0, 1, or 2 at last screen visit.
5. LFTs = AST, ALT, TBili, alkaline phosphatase. ALT >3 x ULN, OR AST >3 × (ULN), OR TBili > 1.5 × ULN (patients with Total Bilirubin up to 2x ULN may be allowed if ALT/AST are within normal limit and investigator has no safety concerns) will exclude a patient from entering the study (see Appendix 4 for liver monitoring information).
6. Serum chemistry = sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, magnesium, phosphorus, LDH, albumin (Central Lab). See Table 4 for laboratory tests.
7. Pregnancy Test: must be negative for women of child bearing capacity at screening.
8. CBC = Hb, HCT, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), RBC, WBC, platelets, differential; Regarding Central Lab Hb values: Two Hb values are obtained at Screening Visit 1 and 2, only 1 of 2 value needs to meet the Hb ≤ 10.0 g/dL criteria.
9. Iron biomarkers = serum iron, ferritin, transferrin, TIBC, TSAT, and UIBC.
10. Exploratory biomarkers (optional) – 2 x 4ml of blood will be collected pre-dose for the preparation of plasma and serum samples for future analysis
11. HRQoL questionnaires will be FACIT-F and FACT-An.
12. Study drug dosing: begins on the first day of dosing (Day 1/Week 1). All study procedures must be completed prior to administration of the 1st dose of study treatment. Dosing should occur at approximately the same time of day. Roxadustat can be taken with water with or without food. The dose of statins should not exceed the protocol-recommended daily dose in the protocol.
13. Dose adjustment review will be performed every 4 weeks for potential upward dose adjustment.
14. Samples for Pharmacokinetics will be taken at times described in the protocol text in Section 8.2.4.2. PK samples will be collected at each dose level for each patient. An “X” in the above table for PK samples on weeks 9 and 13, indicates POTENTIAL days for samples, but will only actually be taken if there is a dose adjustment at that visit and at week 16/EOT if there is a dose adjustment between week 13 and week 16/EOT. If there is only one dose level for a patient during the study then PK is only collected once at week 5.
15. EOT visit should be scheduled at the end of Week 16. Last dose of study drug must be prior to EOT assessments.

Appendix 2. Roxadustat Dose Levels and Dose Adjustment Rules

Dose adjustment will follow as described in the table below. The down titration of the dose is allowed at any time. The maximum dose of study medication is capped at 3.5 mg/kg per dose or 400 mg, whichever is lower. The table below shows all possible dose levels in the study.

Body Weight	Dose Levels					
	Approx. 1.0 mg/kg	Approx. 1.5 mg/kg	Approx. 2.0 mg/kg	Approx. 2.5 mg/kg	Approx. 3.0 mg/kg	Approx. 3.5 mg/kg
45 - <70 kg	50 mg TIW	70 mg TIW	100 mg TIW	150 mg TIW	200 mg TIW*	250 mg TIW*
70-100 kg	100 mg TIW	120 mg TIW	150 mg TIW	200 mg TIW	250 mg TIW	300 mg TIW*
>100 kg	120 mg TIW	150 mg TIW	200 mg TIW	250 mg TIW	300 mg TIW	350 mg TIW*

* Patients body weight MAY require a lower dose than listed in the table above, due to the potential for the maximum dose being exceeded. The dose given should be at one dose level immediately below what is in the above table. In some cases, a dose escalation will NOT be allowed. If a patient requires a further decrease from what is listed in the table above, the medical monitor should be consulted.

If there is **ANY** question as to the appropriate dose to administer contact the CRA or medical monitor.

Dose Adjustment

Following commencement of study treatment, patients are evaluated for response after 4 weeks and the roxadustat dose will be adjusted per the table below. After each dose adjustment, the patient remains on the dose level for a minimum of 4 weeks before further adjustment is permitted.

The following dose adjustment algorithm will apply to patients during the treatment phase of the study. In addition, the down titration of the dose is allowed at any time.

	Hemoglobin (Hb) Values			
Change in Hb from 4 weeks earlier (g/dL)	**Hb <10.5 g/dL**	**Hb 10.5 to 12.0 g/dL**	**Hb >12.0 to <13.0 g/dL**	**Hb ≥13.0 g/dL**
< -1.0 * (or had RBC transfusion within 4 weeks)	↑	↑	No change**	Hold, then resume dosing when: Hb <12 g/dL, at a dose that is reduced by one-dose level **Patients are to return weekly to monitor Hb until dosing can be resumed**
-1.0 to 1.0	↑	No change	↓	
> 1.0	No change	↓	↓	

* A change in Hb from 4 weeks earlier of < -1.0 g/dL means a Hb value that is lower by more than 1.0 g/dL compared to 4 weeks earlier, e.g., a Hb of 9.4 g/dL compared to 10.6 g/dL 4 weeks earlier

** Continue to dose-hold

Dose Reduction

The down titration of the study treatment is allowed at any time per investigator discretion, but a dose reduction must be performed if any of the following criteria are met:

a. Hb >12 g/dL; or
b. Rate of rise of Hb ≥2.5 g/dL over 4 weeks.

Hb levels should be retested for confirmation every 2 weeks after a dose reduction

Reduction should be to one dose level lower than the dose at which the patient is receiving.

****Dose Adjustment for Excessive Hematopoiesis**
At any time during the Treatment Period if Hb increases by ≥2.5 g/dL within 4 weeks, the dose should be reduced by one dose level.

Appendix 3. ECOG Assessment Scale

Grade	ECOG
0	Fully Active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Appendix 4. Liver Function Monitoring

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

Definition of Liver Abnormalities

Confirmed abnormalities should be characterized as follows:

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

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

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

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

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

Follow-up Procedures

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

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

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

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

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

Discontinuation of treatment should be considered if:

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

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

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

Appendix 5. Erythropoiesis-Stimulating Agents (ESAs)

Prohibited ESAs include (but are not limited to) the following:

- darbepoetin
- Mircera (methoxy polyethylene glycol epoetin beta)
- epoetin alfa
- epoetin beta
- epoetin delta
- epoetin theta
- epoetin omega
- hematide

Appendix 6. Roxadustat and Paclitaxel Pharmacokinetics Sub-Study

This optional PK sub-study will investigate the potential effect of Roxadustat timing of administration on the pharmacokinetics of paclitaxel.

Participation in this sub-study is voluntary. Patients are NOT required to participate, and this decision will NOT make them ineligible for the overall study protocol.

Patients who agree to participate in this sub-study will have different timing of Roxadustat dosing in connection with administration of paclitaxel (including Abraxane®) for the duration of the PK sub-study. Roxadustat dosing for these patients will be as follows:

- Dosing of Roxadustat will be separated from paclitaxel administration by approximately 24 hours or 1 day for the initial paclitaxel dose.
- Dosing of Roxadustat will be separated from paclitaxel administration by approximately 48 hours or 2 days for the next paclitaxel dose.
- Dosing of Roxadustat will have no separation from paclitaxel administration (dosed on same day) for the next paclitaxel dose.

Collection of Samples for Paclitaxel PK assessments:

	Paclitaxel Alone	**1-Day Interval between paclitaxel & roxadustat dosing**		**2-Day Interval between paclitaxel & roxadustat dosing**		**Same-Day paclitaxel & roxadustat dosing**
Roxadustat Administration		Roxadustat given 1 Day **before** Paclitaxel	Roxadustat given 1 Day **after** Paclitaxel	Roxadust at given 2-Days **before** Paclitaxel	Roxadustat given 2-Days **after** Paclitaxel	Roxadustat will be administered after collecting pre-transfusion sample
PK Sample Collection	Samples should be collected during screening (before Day 1)	Samples collected on the day of paclitaxel dosing	Samples collected on the day of roxadustat dosing	Samples collected on the day of paclitaxel dosing	Samples collected on the day of roxadustat dosing	Samples collected on the day of paclitaxel/roxadustat dosing
Before start of infusion	X	X		X		X
Within 30 minutes after end of transfusion	X	X		X		X

2 hours after end of transfusion	X	X		X		X*
Before roxadustat dosing			X		X	
1-hour after roxadustat dosing			X		X	
3-hours after roxadustat dosing			X		X	X*

*These samples may be combined if in close proximity

Upon completion of the paclitaxel PK sub study, roxadustat dosing should be held for 24 hours before and after treatment with paclitaxel (time 0 = start of infusion) for the remainder of the study. Roxadustat dosing frequency may be adjusted, as needed.