1 TITLE PAGE

CLINICAL STUDY PROTOCOL	
STUDY TITLE:	A Phase 3 Randomized Double-Blind Placebo-Controlled Study Investigating the Efficacy and Safety of Roxadustat (FG-4592) for Treatment of Anemia in Patients with Lower Risk Myelodysplastic Syndrome (MDS) with Low Red Blood Cell (RBC) Transfusion Burden (LTB)
PROTOCOL NUMBER:	FGCL-4592-082
SPONSOR:	FibroGen, Inc. 409 Illinois Street San Francisco, California 94158, USA
IND NUMBER:	129546
STUDY DRUG:	Roxadustat (FG-4592)
INDICATION:	Anemia due to MDS in International Prognostic Scoring System – Revised Very Low, Low, or Intermediate Risk with <5% Blasts, and has low red blood cell transfusion burden (requires 1 to 4 packed red blood cell units per 8-week period)
FIBROGEN MEDICAL MONITOR:	Name: [redacted] Title: [redacted] Telephone: [redacted] [redacted] Fax: [redacted] E-mail: [redacted]
PROTOCOL VERSION AND DATE:	ORIGINAL: 03 FEBRUARY 2017 AMENDMENT 01: 27 MARCH 2017 AMENDMENT 02: 16 MAY 2018

INVESTIGATOR SIGNATURE PAGE

STUDY ACKNOWLEDGEMENT

A Phase 3 Randomized Double-Blind Placebo-Controlled Study Investigating the Efficacy and Safety of Roxadustat (FG-4592) for Treatment of Anemia in Patients with Lower Risk Myelodysplastic Syndrome (MDS) with Low Red Blood Cell (RBC) Transfusion Burden (LTB)

FGCL-4592-082

IND 129546

INVESTIGATOR STATEMENT

I have read the protocol dated 16 May 2018, including all appendices and the current Investigator's Brochure (IB), and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

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

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

Investigator Name (Printed)	Institution Name and Address
Signature	Date

FG-4592 Investigator Brochure Version 9.0

Please retain the original for your study files.

SUMMARY PROTOCOL AMENDMENT CHANGES

Amendment 02

Section(s) Affected	Description of Change	Rationale for Change
Entire Document	AMENDMENT 02: 16 MAY 2018	Updated document header and all references from Amendment 1: 27 March 2017 to Amendment 2: 16 May 2018
Entire Document	Corrected minor typographical and grammatical errors	Administrative changes and errors from previous version of the protocol
Entire Document	Replaced ~~step~~ with **level**	Provided for additional clarity and details
Title Page – FibroGen Medical Monitor	Replaced [redacted] with [redacted] telephone, mobile and email address	Updated FibroGen Medical Monitor
Table of Contents	Added **Sections 3.6, 3.6.1, 3.6.2**	Added the following sections for additional clarity and details. 3.6 Blinding 3.6.1 Maintenance of Blinding 3.6.2 Planned and Unplanned Unblinding of Treatment Assignment
List of Abbreviations	Updated list of abbreviations	Added and deleted abbreviations not included in previous version of the protocol or no longer relevant
Protocol Synopsis – Number of Patients:; Section 2.5; Appendix C	Inserted – **approximately**	Provided for additional clarity
Protocol Synopsis – Study Design Overview (cont.):; Section 3.3.1	Inserted – **Approximate** and **Patient Weight** in Starting Dose Table	Provided for additional clarity and details

Section(s) Affected	Description of Change	Rationale for Change
Protocol Synopsis – Study Design Overview (cont.):; Protocol Synopsis – Inclusion Criteria:; Section 3.1.1; Section 4.1; Section 6.1; Appendix A: Footnote 5	Replaced of ~~≥ 16 weeks duration,~~ ~~within 16 weeks~~ and ~~(documented within 16 weeks prior to randomization)~~ with **There is no minimum time from diagnosis to registration/randomization except to allow for proper IPSS-R classification to be made, and to show transfusion dependence for patients in both portions of the study**	Change in enrollment criteria for greater flexibility in patient enrollment
Protocol Synopsis – Study Design Overview: Screening Period:; Protocol Synopsis – Inclusion Criteria; Section 3.1; Section 3.1.1; Section 3.3.1; Section 3.4.5; Section 3.4.6; Section 4.1	Inserted – **registration/randomization**	Provided for additional clarity and details
Protocol Synopsis – Study Design Overview (cont.):; Protocol Synopsis – Inclusion Criteria; Section 3.1.1; Section 4.1; Section 6.1; Appendix A Footnote 11	Inserted – **Open-Label patients only, the requirement to demonstrate transfusion dependence can also be met by a principle investigator starting this particular patient on pRBC transfusion during the screening period**	Change in enrollment criteria for greater flexibility in patient enrollment
Protocol Synopsis – Study Design Overview (cont.):; Section 3.1; Appendix A: Footnote 15	Inserted – **The roxadustat dose per body weight are estimates only and the exact dose will be assigned per body weight ranges as shown in the body of the protocol** Replaced ~~Patient Reported Outcomes (PRO) assessments~~ with **Health-related quality of life (HRQoL) questionnaries**	Provided for additional clarity

Section(s) Affected	Description of Change	Rationale for Change
Study Design Overview (cont.): Treatment:; Protocol Synopsis – Inclusion Criteria:; Protocol Synopsis – Best Supportive Care:; Section 3.4.3; Section 4.1; Section 6.1; Appendix A: Footnote 11	Inserted – **The Principle Investigator (PI) and site staff will utilize their own institutional criteria for the determination of when to transfuse a patient.**	Provided for additional clarity
Study Design Overview (cont.): Treatment:;	Inserted – **Documentation of standard site transfusion criteria will be documented in overall study files** Inserted – **transfusion**	Provided for additional clarity and details
Study Design Overview (cont.):; Pharmacokinetics/Pharmacodynamics (PK/PD):; Appendix A: Footnote 3; Appendix J	Replaced ~~self~~ and ~~home or at~~ with **the clinic**	Updated to increase flexibility in patients' PK blood draw schedule for Week 5 and Week 21 based on Investigational Product availability during the PK time points
Protocol Synopsis – Inclusion Criteria:; Section 4.1; Table 2: Additional Study Procedures/ Assessments and Blood Sampling by Visit for the 52-Week Treatment Period and Post-EOT (Appendices A, B, K); Appendix A: Table; Appendix B	Replaced ~~Bone marrow aspirate/biopsy~~ with **Bone marrow aspirate and biopsy**	Provided for additional clarity and details

Section(s) Affected	Description of Change	Rationale for Change
Protocol Synopsis – Inclusion Criteria:; Section 4.1	Replaced 1. ~~No prior use of recombinant erythropoietins or analogues (erythropoiesis-stimulating agents, ESAs), or received a life-time ESA exposure of less than 28 days, AND received no ESA within the 12 weeks prior to day 1 randomization~~ with 1. **There is no restriction on** prior use of recombinant erythropoietins or analogues (erythropoiesis-stimulating agents (ESAs))**, except that the patient must not have received any ESA within the 8 weeks prior to Day 1 registration/randomization.**	Change in enrollment criteria for greater flexibility in patient enrollment
	Replaced ~~4. Pre-transfusion Hb ≤10.0 g/dL during Screening~~ with 4. Hb ≤10.0 g/dL during Screening. **Hb values are obtained at Screening Visit 1 and 2; only 1 value needs to meet the Hb < 10.0 g/dL criteria. These values must be the Central Laboratory values. A third value may be obtained if necessary.**	Provided for additional clarity and details
Protocol Synopsis – Inclusion Criteria:; Section 4.1 Appendix A: Footnote 7	Replaced 7. ~~ECOG performance status of 0 or 1 at last screen visit (Appendix F)~~ with **ECOG performance status of 0, 1 or 2 at last screen visit (Appendix F)**	Change in enrollment criteria for greater flexibility in patient enrollment
Protocol Synopsis – Exclusion Criteria; Section 4.2; Appendix A: Footnote 8	~~Alanine aminotransferase (ALT) AND aspartate aminotransferase (AST) >3 × upper limit of normal (ULN), and total bilirubin (Tbili) > 1.5 × ULN (Appendix H)~~ Alanine aminotransferase (ALT) >3 x upper limit of normal (ULN), **OR** aspartate aminotransferase (AST) >3 × ULN, **OR** total bilirubin (TBili) > 1.5 × ULN (see Appendix H)	Text updated to be in line with Appendix H

Section(s) Affected	Description of Change	Rationale for Change
Protocol Synopsis – Exclusion Criteria:; Section 4.2	Inserted in Exclusion 10 – **for more than 7 days** Inserted in Exclusion 11 – **as determined by the investigator** Replaced in Exclusion 12 ~~Active infection(s) requiring antibiotic therapy~~ with **Active infections(s) requiring systemic antibiotic therapy** Inserted in Exclusion 15 – **e.g., warfarin or enoxaparin, a factor Xa inhibitor such as rivaroxaban or apixaban, or a direct thrombin inhibitor such as dabigatran. Chronic use of low-dose aspirin is allowed.** Replaced in Exclusion 23 ~~patients with a history of cured malignancy with no evidence of malignancy for at least 5 years are eligible~~ with **patients with a history of cured malignancy with no evidence of recurrence for at least 3 years are eligible** Inserted – **25. Pregnant or breastfeeding females**	Provided for additional clarity and details Change in enrollment criteria for greater flexibility in patient enrollment Updated Exclusion Criteria
Protocol Synopsis – Exclusion Criteria:; Section 4.2 Appendix L	Replace ~~Creatinine Clearance~~ with **Creatinine Clearance/eGFR**	Provided for additional clarity and details
Protocol Synopsis – Efficacy Endpoints and Assessments (double-blind):; Section 2.8.2; Section 8.3.3.2.4	Replaced Proportion of Patients who achieve TI for ≥20 weeks (~~140 consecutive days~~) with **(120 consecutive days)**	Calculation error from previous version of the protocol
Protocol Synopsis – Statistical Methods (cont.): Data Safety Monitoring Board (DSMB); Section 3.6	Inserted – **prior to the start of the DB portion of the study** Inserted – **likely**	Provided for additional clarity
Figure 3	Study Schemas updated	Updated in line with updated protocol enrollment criteria

Section(s) Affected	Description of Change	Rationale for Change
Section 3.3.1	Inserted – **at a ratio of 3:2 to roxadustat or placebo**	Provided for additional clarity and details
Section 3.3.2	Inserted – **There are two periods for the study drug dosing – the correction phase and the maintenance phase.** Inserted – **Correction phase:** Inserted – **Maintenance Phase:** Inserted – **Given the complexities of the dose adjustment algorithm, and the need to take into consideration various clinical parameters, it is not considered a protocol deviation when study subjects are dosed based on their clinical circumstance, whether or not this is concordant with the roxadustat dosing algorithm, unless it is related to "excessive hematopoiesis" or "Overdose" (prescribed 400 mg or > 3.5 mg/kg/dose).**	Provided for additional clarity and details Provided for additional clarity and details
Section 3.3.2; Section 8.3.3.2	Section moved from Section 3.3.2 Dose Adjustments to Section 8.3.3.2 Analysis of the Secondary Efficacy Endpoints	Paragraph originally in wrong section of the previous version of the protocol
Section 3.4.1	Replaced ~~To avoid confounding effects on study endpoints, changes to anti-hypertensive medications should be minimized, and only if deemed necessary by the Investigator~~ with To avoid confounding effects on study endpoints, changes **in administration of chronic concomitant** medications should be minimized and **done** only if deemed necessary by the **Principal** Investigator	Provided for additional clarity and details
Section 3.4.5	Inserted – **except for ESAs which are prohibited for 8 weeks prior to Week 1 Day 1 of registration/randomization visit and at any time during the study (see first bullet below regarding ESAs)**	Change in enrollment criteria for greater flexibility in patient enrollment
Section 4.3; Appendix O	Replaced ~~should be considered~~ with **will occur**	Text updated to be in line with Appendix H
Section 4.3	Inserted – **Treatment with ESAs**	Provided for additional clarity and details

Section(s) Affected	Description of Change	Rationale for Change
Section 4.6; Section 4.6.1; Section 4.6.2	Added the following sections for additional clarity and details. 3.6 Blinding 3.6.1 Maintenance of Blinding 3.6.2 Planned and Unplanned Unblinding of Treatment Assignment	Provided for additional clarity for blinding in the double-blind portion of the study
Section 5.1	Inserted – **Placebo tablets are identical to the roxadustat tablets except for the absence of active roxadustat**	Provided for additional clarity and details
Section 6.1	Replaced ~~SAEs will be recorded~~ with **AEs and SAEs will be recorded in the medical record** Inserted – **SAEs will be reported to FibroGen**	Provided for additional clarity and details
Section 6.3.1.1; Section 6.8	Replaced ~~Local hemoglobin level (hemocue device, Day 1 and all visits beyond) and Central Hb level~~ with **Local hemoglobin level (hemocue device is encouraged but not required)**	Updated to increase flexibility for sites' method of local Hb blood draws with the intention that patients will receive same day Hb results for dose adjustment purposes
Section 6.3.1.2	Inserted – **, EOT and Post-EOT** Inserted – **All blood samples must be drawn prior to dose unless otherwise noted (e.g. certain PK draws).**	Provided for additional clarity and details

Section(s) Affected	Description of Change	Rationale for Change
Table 2: Additional Study Procedures/ Assessments and Blood Sampling by Visit for the 52-Week Treatment Period and Post-EOT (Appendices A, B, K)	Inserted in Week 9 – **Assess erythroid response** Added **4 Weeks Post-EOT** • Procedures and Assessments ○ **Physical Exam** ○ **ECOG score** ○ **Vital signs (BP, HR, RR, and Temp)** ○ **Health-related quality of life (HRQoL) assessments** ○ **ECG** • Blood Samples ○ **CBC (central) and Local Hb** ○ **Serum chemistries** ○ **LFTs** ○ **Iron biomarkers** ○ **Hepcidin** ○ **Endogenous serum EPO level** ○ **PT, PTT** ○ **Serum lipid panel** ○ **B_{12} and folate** ○ **C-reactive protein** ○ **Reticulocytes & CHr** ○ **Serum pregnancy (for females of childbearing capability)** Added **If Early Termination, every 8 weeks assessment from 4 Weeks Post-EOT visit. Last visit at Week 52 from first dose.** • Procedures and Assessments ○ **Vital signs (BP, HR, RR, and Temp)** • Blood Samples ○ **CBC (central) and Local Hb** ○ **Serum chemistries** ○ **LFTs** ○ **Iron biomarkers** ○ **Hepcidin** ○ **Endogenous serum EPO level**	Provided for additional clarity and details
Table 2: Additional Study Procedures/ Assessments and Blood Sampling by Visit for the 52-Week Treatment Period and Post-EOT (Appendices A, B, K); Appendix A: Table	Added **Point-of-care Urine Pregnancy (for females of child-bearing capabilities)** • **Week 13** • **Week 25** • **Week 39**	To be able to detect any pregnancy in women of childbearing potential

Section(s) Affected	Description of Change	Rationale for Change
Section 7.3.8	Replaced ~~Gradual worsening of MDS should be considered disease progression and should not be reported as an AE during the study~~ with Gradual worsening of MDS should be considered disease progression and should **be reported as an AE during the study. Worsening of anemia, per se, should not be reported as disease progression because changes in Hb levels will be adequately monitored and assessed in the efficacy analyses.**	Provided for additional clarity
Appendix A; Appendix B	Updated numbering of Appendix A Footnote	To ensure alignment between footnotes, tables and appendices
Appendix A: Footnote 2	Deleted – **2. If participant is known positive for any (hepatitis B, hepatitis C, HIV), no need to repeat test** Inserted – **Serum erythropoietin level must be ≤400 mIU/mL at screening; during the last month of treatment a serum EPO level will be drawn just prior to the next study drug dosing; patients should be told to not take their study drug until after the study visit on that day.** Deleted – **Serum B12 and folate must be >lower limit of normal at screen**	Omitted for clarity from previous version of the protocol Included in error from previous version of the protocol
Appendix A: Footnote 5	Replaced ~~within 16 weeks prior to Enrolment/randomization~~ with **for the IPSS-R criteria**	Change in enrollment criteria for greater flexibility in patient enrollment
Appendix A: Footnote 6	Inserted – **Weight at registration/randomization will be used for determination of starting dose.**	Provided for additional clarity and details
Appendix A: Footnote 10	Replace ~~11. Pregnancy Test: must be negative for women of child bearing potential as screening~~ with **10. Pregnancy Test: must be negative for women of child bearing capacity at screening. Additional pregnancy testing for women of child bearing capacity will also be done at Weeks 13, 25, 39, EOT and Post-EOT visits.**	To align with Exclusion 25

Section(s) Affected	Description of Change	Rationale for Change
Appendix A: Footnote 12	Deleted – **at screening, platelets cannot be <100,000/mm^3 and ANC <1500/mm^3; a local (Hemocue) will be drawn at each visit** Inserted – **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.**	Included in error in previous version of the protocol Provided for additional clarity and details
Appendix A: Footnote 13	Deleted – **Serum ferritin >50 ng/mL at screen**	Included in error in previous version of the protocol
Appendix A: Footnote 14	Inserted – **which should be given at the site**	Provided for additional clarity and details
Section 3.4.1.1; Appendix A: Footnote 16	Deleted – **Patients should be advised that study medication be taken at least one hour before or three hours after their phosphate binder if possible**	Removal of phosphate dosing restriction
Appendix A: Footnote 18	Inserted – **A re-assessment will be done for these patients at Week 12 and if TI is observed the dose will not be increased**.	Added for consistency through the protocol
Appendix C: Dose Reduction	Replaced ~~After patient has achieved TI for at least 8-weeks, or has undergone treatment with the maximum allowable dose, i.e., 400 mg TIW or 3.5 mg/kg for at least 8-weeks, and there were no change in erythroid response compared to the previous 8-weeks at a lower dose level, patient may undergo dose reduction by 1-dose step~~ with **In the instance where the patient achieved TI in the initial 8-weeks of the study,** or has undergone treatment with the maximum allowable dose, i.e., 400 mg TIW or 3.5 mg/kg for at least 8-weeks, patient may undergo dose reduction by 1-dose level.	Provided for additional clarity and details
Appendix D	Inserted – **8 weeks** Inserted – **RBC** Replaced ~~< 1.0 (or had transfusion within 4 weeks)~~ with **< 1.0 * (or had RBC transfusion within 4 weeks)** Inserted – ***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**	Provided for additional clarity and details

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LIST OF ABBREVIATIONS

Abbreviation	Definition
~	approximately
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
ANCOVA	analysis of covariance model
AST	aspartate aminotransferase
BP	blood pressure
BSC	best supportive care
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
CHr	reticulocyte hemoglobin content
CRP	C-reactive protein
CI	confidence interval
CKD	chronic kidney disease
CMH	Cochran-Mantel-Haenszel
CS	clinically significant
CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
DB	double-blind
DD	dialysis-dependent
DD-CKD	dialysis-dependent chronic kidney disease
DILI	drug-induced liver injury
DSMB	Data and Safety Monitoring Board
DVT	deep vein thrombosis
EC	Ethics Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOS	end of study
EOT	end of treatment
EPO	erythropoietin
EQ-5D	European Quality of Life (EuroQol) five-dimension health questionnaire
ER	emergency room

Abbreviation	Definition
ESA	erythropoiesis-stimulating agent
ESMO	European Society for Medical Oncology
ESRD	end-stage renal disease
ET	early termination
FACT-An	Functional Assessment of Cancer Therapy – Anemia
FACT-F	FACT-Fatigue, a subset of FACT-An
FDA	US Food and Drug Administration
FAS	full analysis set
G-CSF	granulocyte colony stimulating factor
GCP	Good Clinical Practice
GFR	glomerular filtration rate
Hb	hemoglobin
HBsAg	hepatitis B surface antigen
HCT	hematocrit
HCV	hepatitis C virus
HIF	hypoxia-inducible factor
HIF-PH	HIF prolyl hydroxylase
HIF-PHI	HIF prolyl hydroxylase inhibitor
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HMA	hypomethylating agent
HR	heart rate
HRQoL	health-related quality of life
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
INR	international normalized ratio
IPSS-R	International Prognostic Scoring System – Revised
IRB	Institutional Review Board
ITT	Intent to Treat Population
IV	intravenous
LDH	lactate dehydrogenase
LDL	low density lipoprotein
LLN	lower limit of normal
LFT	liver function test
LTB	low transfusion burden
MDS	myelodysplastic syndrome

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model repeat measures
N (or n)	sample size
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCS	not clinically significant
NDD-CKD	non dialysis-dependent chronic kidney disease
NIH	National Institute of Health
NYHA	New York Heart Association
OL	open-label
PD	pharmacodynamics
PE	physical exam
PI	Principal Investigator
PK	pharmacokinetics
PPS	per protocol set
pRBC	packs of red blood cells
PROMIS	Patient-Reported Outcomes Measurement Information System
PT, PTT	prothrombin time, partial thromboplastin time
RBC	red blood cell
QALY	quality adjusted life year
rhEPO	recombinant human erythropoietin
RR	respiratory rate
SAE	serious adverse event
SAF	safety analysis set
SAP	Statistical Analysis Plan
SCT	stem cell transplant
SEER	surveillance, Epidemiology, and End Results Program of the US National Cancer Institute
TBili	total bilirubin
TEAE	treatment-emergent adverse event
TG	triglycerides
TI	transfusion-independent
TIA	transient ischemic attack
TIBC	total iron binding capacity
TIW	three times weekly
TQT	thorough clinical study of QT/QTc interval prolongation
TSAT	transferrin saturation
UIBC	unsaturated iron binding capacity
ULN	upper limit of normal
US	United States

Abbreviation	Definition
VEGF	vascular endothelial growth factor
VHL	von Hippel-Lindau protein
WBC	white blood cell
WHODrug	World Health Organization Drug Dictionary

PROTOCOL SYNOPSIS

Study Title:	A Phase 3 Randomized Double-Blind Placebo-Controlled Study Investigating the Efficacy and Safety of Roxadustat (FG-4592) for Treatment of Anemia in Patients with Lower Risk Myelodysplastic Syndrome (MDS) with Low Red Blood Cell (RBC) Transfusion Burden (LTB)
Protocol Number:	FGCL-4592-082
Investigational Product:	Roxadustat (FG-4592)
Target Population:	Adult patients with International Prognostic Scoring System – Revised (IPSS-R) very low risk, low risk, or intermediate risk MDS with <5% bone marrow blasts (lower-risk MDS), and has low RBC transfusion burden (requires 1 to 4 packs of RBC [pRBC] per 8-week period)
IND Number:	129546
Study Phase:	Phase 3
Study Centers Planned:	Approximately 80
Number of Patients Planned:	Up to 24 patients will be enrolled in sequential dose level cohorts (approximately 1.5, 2.0, or 2.5 mg/kg of Roxadustat – by body weight at registration visit) prior to start of the double-blind portion of the study. Randomized double-blind placebo-controlled along with best supportive care (BSC) – 160 patients; 3:2 randomization (96:64; roxadustat:placebo)
Primary Objectives:	Evaluate the efficacy of roxadustat in the treatment of anemia in patients with lower risk MDS who have a low burden of RBC transfusion.
Secondary Objectives:	• Evaluate the safety of roxadustat • Evaluate the impact of roxadustat on RBC transfusion requirements • Evaluate pharmacokinetics (PK) and pharmacodynamics (PD) of roxadustat in MDS patients • Evaluate effect of roxadustat on quality of life parameters
Study Design Overview:	The study consists of two components. An open-label (OL) lead-in component to identify the optimal starting dose for the double-blind (DB) phase followed by a DB component comparing treatment with roxadustat with placebo along with best supportive care (BSC). The study duration for patients in both the OL and DB components is 52

Study Design Overview (cont.):	weeks. A primary efficacy assessment will be made in the DB component when all randomised patients have completed 28 weeks DB treatment or have discontinued. Unless indicated, the same procedures will apply in both components of the study. In the OL lead-in component, up to 24 patients will be enrolled in sequential dose level cohorts (n=8) prior to the start of the DB portion of the study. All patients will receive roxadustat in an OL manner. The first 8 patients will receive a starting dose of 1.5 mg/kg. The next 8 patients will receive a starting dose of 2.0 mg/kg. The last 8 patients will receive a starting dose of 2.5 mg/kg. The roxadustat dose per body weight are estimates only and the exact dose will be assigned per body weight ranges as shown in the body of the protocol. Upon enrolling the OL component of the study, approximately 160 patients will be randomized in the DB placebo controlled portion of the study. **Screening Period:** All screening procedures are to be completed within 28 days prior to Day 1 of Treatment, except for documentation of the following which can be obtained from patients' medical records: 1. Lower risk MDS (IPSS-R very low risk, lower risk, or intermediate risk). There is no minimum time from diagnosis to registration/randomization except to allow for proper IPSS-R classification to be made, and to show transfusion dependence for patients in both portions of the study. 2. Results from bone marrow examination and cytogenetic analysis performed within 16 weeks prior to Day 1 of treatment can be used. The required bone marrow slides and report must be available for a centralized review at any time throughout the study. 3. Patients are deemed to have low RBC transfusion burden (LTB) if they received 1 to 4 documented pRBC transfusions within 8 weeks prior to registration/randomization. Patients with 1 pRBC/8-weeks must have a documented history of requiring 1 pRBC/8-weeks in 2 consecutive periods of 8 weeks in the 16 weeks preceding registration/ randomization. Pre-transfusion and post-transfusion hemoglobin (Hb) levels within 8 weeks prior to Day 1 of treatment will also be recorded. The percentage of patients having 1pRBC transfusion at baseline will be capped at 30% for the DB portion of the study. **Open-Label patients only**, the requirement to demonstrate

Study Design Overview (cont.):

transfusion dependence can also be met by a principal investigator (PI) starting this particular patient on pRBC transfusion during the screening period.

Patients must meet all inclusion and none of the exclusion criteria to be eligible for the OL or the DB components of the study.

Treatment:

Up to 24 patients will be enrolled in sequential dose level cohorts prior to start of the DB portion of the study. All patients will receive roxadustat in an OL manner. The first 8 patients will receive a starting dose of 1.5 mg/kg (Dose Level 1). The next 8 patients will receive a starting dose of 2.0 mg/kg (Dose Level 2). The last 8 patients will receive a starting dose of 2.5 mg/kg (Dose Level 3).

The starting dose table for the OL component of the study is shown below.

Dose Level Group	Approximate Roxadustat dose level (mg/kg)	Patient Weight		
		45 to <70 kg	70 - 100 kg	> 100 kg
1	1.5	70 mg TIW	120 mg TIW	150 mg TIW
2	2.0	100 mg TIW	150 mg TIW	200 mg TIW
3	2.5	150 mg TIW	200 mg TIW	250 mg TIW

The OL is intended to optimize the starting dose for the subsequent DB portion of the study in which, 160 eligible lower risk MDS patients with LTB will be randomized 3:2 to roxadustat or matching placebo. It is anticipated that the starting dose level will be Dose Level 2 (2.0 mg/kg) and the protocol is written to reflect this but if the OL data identifies Dose Level 1 or 3 as a more optimal starting dose, this will be implemented.

Patients in the DB component of the study will be randomized with the following stratifications:

- Serum erythropoietin (EPO) level: either ≤200 mIU/mL OR >200 mIU/mL and ≤400 mIU/mL
- IPSS-R low risk /very low risk vs. intermediate risk group classification
- RBC transfusion burden: 1 pRBC/8-weeks over 16 consecutive weeks vs 2-4 pRBC/8-weeks

The PI and site staff will utilize their own institutional criteria for the determination of when to transfuse a patient. Documentation of

Study Design Overview (cont.):	standard site transfusion criteria will be documented in overall study files. For all patients (OL and DB components), dose adjustments/escalations will occur every 8 weeks at pre-defined dose level increments, with the exception that the starting dose will be maintained if an erythroid response (defined as a 50% reduction in pRBC transfusion from baseline) is seen after the initial 8 weeks of dosing. A re-assessment will be done for these patients at week 12 and if transfusion independence (TI) is observed the dose will not be increased. If TI is NOT observed at this point, the dose will be increased by one dose level. See Appendix C for details on dosing and dose escalation. Once TI for at least 8 continuous weeks has been achieved, Maintenance Phase will begin and the study drug dose should follow guidance described in Appendix D. During the course of the study, visits and assessments will be performed as defined in the schedule of assessments (see Appendix A and Appendix B). The overall study duration is 52 weeks with primary efficacy assessment after the first 28 weeks in the DB component, and continued treatment up to 52 weeks. The OL portion patients who receive roxadustat may remain in the study up to 52 weeks of treatment based on investigator discretion, adequate safety, and impression of benefit. These patients will undergo all procedures as the randomized patients in the DB study with the exception of not completing the Health-related quality of life (HRQoL) questionnaires. When all the randomized (DB) patients complete 28 weeks of treatment or are discontinued from study medication before this time, the analysis of the primary and secondary efficacy endpoints will occur. Only Sponsor personnel who are not directly involved with the study sites/patients will have access to the unblinded data. The blind will be maintained for study patients, PI, site staff and site monitoring personnel for the remainder of the study (to Week 52 plus a 4 week follow-up period). **Follow-Up:** All patients who complete 52 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) will remain in the study through the entire 52 week study period. Patients will have a 4 week follow-up visit after stopping study medication and then be followed up at a reduced visit schedule of every 8 weeks

	after the follow-up visit until the end of the study. **Pharmacokinetics/Pharmacodynamics (PK/PD):** Blood samples will be collected at the study site for determination of roxadustat plasma concentrations and erythropoietin levels at 1-3 and 3-5 hours after dosing at clinic on Day 1 (Week 1) as well as 4-6 hours at Week 5 and 8-10 hours at Week 21 after administration at the clinic. Two samples will be obtained 0-2 hours before dosing and 2-3 hours after dosing at Week 25. Hepcidin levels will also be measured at selected timepoints.
Inclusion Criteria:	1. Diagnosis of primary MDS (confirmed by bone marrow aspirate and biopsy prior to Treatment Day 1), classified by the IPSS-R as very low, low, or intermediate risk with <5% bone marrow blasts. There is no minimum time from diagnosis to registration/randomization except to allow for proper IPSS-R classification to be made, and to show transfusion dependence for patients in both portions of the study. 2. RBC transfusion requirement of either a. 2 to 4 pRBC over the 8-weeks prior to registration/randomization, or b. 1 pRBC during the 8-weeks prior to registration/randomization. Patients with 1 pRBC must have a documented history of requiring 1pRBC/8-weeks in 2 consecutive periods of 8 weeks in the 16 weeks preceding registration/randomization c. The PI and site staff will utilize their own institutional criteria for the determination of when to transfuse a patient. d. **Open-Label patients only**, the requirement to demonstrate transfusion dependence can also be met by a PI starting this particular patient on pRBC transfusion during the screening period. 3. There is no restriction on prior use of recombinant erythropoietins or analogues (erythropoiesis-stimulating agents (ESAs)), except that the patient must not have received any ESA within the 8 weeks prior to Day 1 registration/randomization. ESAs include but are not limited to any recombinant human erythropoietin and other drugs listed in Appendix I. 4. Hb ≤10.0 g/dL during Screening. Hb values are obtained at

	Screening Visit 1 and 2; only 1 value needs to meet the Hb ≤ 10.0 g/dL criteria. These values must be the Central Laboratory values. A third value may be obtained if necessary. 5. Age ≥18 years 6. Body weight ≥45 kg 7. ECOG performance status of 0, 1 or 2 at last screen visit (Appendix F) 8. Must be capable of giving written informed consent
Exclusion Criteria:	1. Diagnosis of secondary MDS associated with prior chemotherapy, extensive radiation therapy (>25% of bone marrow reserve), and or/other significant chemical or radiation exposure 2. Previous diagnosis of IPSS-R high risk or very high risk MDS (Appendix G) 3. Planned myeloablative or craniospinal radiation during the study 4. Prior bone marrow or stem cell transplantation (SCT) 5. Significant myelofibrosis (>2+ fibrosis) 6. MDS associated with 5q(del) cytogenetic abnormality 7. Screen serum erythropoietin level >400 mIU/mL 8. Alanine aminotransferase (ALT) >3 x upper limit of normal (ULN), **OR** aspartate aminotransferase (AST) >3 × ULN, **OR** total bilirubin (TBili) > 1.5 × ULN (see Appendix H) 9. Azacitidine, decitabine, thalidomide, lenalidomide, granulocyte colony-stimulating factor (G-CSF), or luspatercept, or any investigational drugs within 8-weeks prior to Day 1 Treatment or plans to use any of these medications during the course of clinical trial participation 10. Anticipated use of dapsone at any dose amount or chronic use of acetaminophen or paracetamol > 2.0 g/day during the study for more than 7 days 11. Clinically significant anemia, as determined by the investigator, due to non-MDS etiologies such as iron deficiency, vitamin B_{12} or folate deficiency, autoimmune or hereditary hemolysis or anemia or hemorrhage or hereditary anemia such as sickle cell anemia or thalassemia 12. Active infection(s) requiring systemic antibiotic therapy 13. Cockroft-Gault calculated estimated glomerular filtration rate (eGFR) <30 mL/min 14. Thromboembolic event (such as deep vein thrombosis (DVT)), pulmonary embolism, myocardial infarction, stroke, or transient

Exclusion Criteria (cont.):	ischemic attack (TIA), within previous 6 months 15. Current condition requiring anticoagulant, e.g., warfarin or enoxaparin, a factor Xa inhibitor such as rivaroxaban or apixaban, or a direct thrombin inhibitor such as dabigatran. Chronic use of low-dose aspirin is allowed. 16. 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 17. Clinically significant or uncontrolled ongoing inflammatory/autoimmune disease (e.g., rheumatoid arthritis, Crohn's disease, celiac disease, etc.) 18. History of significant liver disease or active liver disease 19. Major surgery planned during the treatment period 20. Known, active or chronic gastrointestinal bleeding 21. Known human immunodeficiency virus (HIV), hepatitis B or hepatitis C infection 22. 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 23. History of leukemia or other active malignancy except localized and non-metastatic squamous or basal cell carcinoma of the skin, or cervical intraepithelial neoplasm; patients with a history of cured malignancy with no evidence of recurrence for at least 3 years are eligible 24. Previous recipient of roxadustat or another hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) 25. Pregnant or breastfeeding females
Study Procedures:	See Schedule of Assessments (Appendix A and Appendix B)
Investigational Product:	**Roxadustat** Tablets with strengths of 20 mg, 50 mg ,100 mg and 150 mg **Route of Administration:** Oral (all tablets must be administered whole)
Comparator:	Placebo will be similar in appearance to the investigational product and matching the dose strengths of the investigational product.
Best Supportive Care:	Best supportive care (BSC) including RBC transfusion is permitted to ensure patient's safety. The PI and site staff will utilize their own

	institutional criteria for the determination of when to transfuse a patient. Use of any ESA (epoetin alfa, epoetin beta, darbepoetin or others) during the study is not permitted (see Appendix I) and patients who receive an ESA will be discontinued from further treatment with study medication. Patients who discontinue study medication early (for any reason) will remain in the study through for the 52 week study period. Patients will have a 4 week follow-up visit after stopping study medication and then will be followed up at a reduced visit schedule of every 8 weeks until the end of the study.
Efficacy Endpoints and Assessments (DB):	**Primary Efficacy Endpoint:** The primary efficacy endpoint is the proportion of patients who achieved transfusion-independence (TI) ≥56 consecutive days in the first 28 weeks of treatment **Secondary Efficacy Endpoints (all secondary and exploratory endpoints will be analyzed at both for the first 28 weeks of treatment and for the end of the 52-week study treatment period):** • Proportion of patients who achieved ≥50% reduction in number of RBC transfusion over any 8 weeks compared to their baseline • Cumulative number of patient-exposure-week of TI • Cumulative number of pRBC packs transfused • Proportion of patients who achieved TI for ≥20 Weeks (140 Days) • Mean change from baseline in Physical Function as measured by Patient Reported Outcomes Measurement Information System (PROMIS) • Mean change from baseline in PROMIS Fatigue score. • Mean change from baseline in Euroqol Quality of Life Five Dimensional Five Level Health Questionnaire (EQ-5D-5L) assessment **Exploratory endpoints:** • Duration of transfusion independence • Proportion of patients who achieve a mean Hb increase of ≥1.0 g/dL and ≥1.5 g/dL (averaged over 8 weeks in those that achieved TI) compared to pre-transfusion Hb at baseline • Potential impact of baseline endogenous erythropoietin levels on roxadustat treatment response and dose requirement

	• Effect on hepcidin and iron metabolism • Effect on cholesterol and lipid parameters **Additional Exploratory Efficacy Endpoints:** Additional exploratory efficacy endpoints are described in the statistical analysis plan and will use the Full Analysis Set (FAS) population.
Safety Assessments:	• Adverse events (AE) and serious adverse events (SAEs) reporting • N (%) patients with progression to acute myeloid leukemia (AML) • Clinical laboratory measures, including hemoglobin and liver function tests (LFTs) (AST, ALT, total bilirubin (TBili) and alkaline phosphatase(ALP)) • Heart rate, blood pressure and electrocardiogram (ECG)
PK/PD Biomarkers & Other Labs:	• Measurements of PK, serum erythropoietin levels • Measurements of iron indices including serum iron, ferritin, transferrin or total iron binding capacity (TIBC), saturation and hepcidin • Measurements of lipids/cholesterol levels
Statistical Methods:	Data from patients in the OL component will be analyzed separately from the DB randomized component of the study. **DB Component:** Descriptive statistics including number of patients (N), means, standard deviations, medians, and minimum and maximum values will be presented for continuous variables. Counts and percentages will be presented for categorical variables. For efficacy endpoints, the standard error and 95% confidence intervals will be presented as part of the descriptive summaries. The following analysis sets are defined and will be used for the statistical analysis: • Full Analysis Set (FAS) • Safety Analysis Set (SAF) The FAS Population consists of all patients **randomized** to the study. This is the population used for the efficacy analyses. The Safety Population consists of all patients who have received at least one dose of study drug. Analyses of the safety data will be based on the Safety Populations. Baseline Hb value for efficacy analysis is defined as the mean of Screening central laboratory Hb value and Day 1 Hb value.

Statistical Methods (cont.):	**Data Analyses** 160 patients will to be randomized in a 3:2 ratio to roxadustat or matching placebo. This sample size will provide at least 90% power to demonstrate a statistically significant difference between roxadustat and placebo at the significance level of 0.05 using a two-sided Fisher's test, and assuming the response rates of the primary endpoint are 35% and 5% in roxadustat and placebo, respectively. The primary endpoint of the study will be compared between the two treatment groups using the Cochran-Mantel-Haenszel (CMH) chi-square test, controlling for stratification factors. If one or more of the levels of the stratification variables are underrepresented during enrollment resulting one or more of the (2×2×2) 8 strata having with too few patients to meet the required per-strata sample size for the planned statistical methodology then the stratification variable with the highest imbalance will not be included in the analysis. This practice will be followed for the primary, secondary and exploratory variables. Categorical endpoints will be analyzed using the CMH test. Cox regression model will be used to analyze time-to-event endpoints. Analyses will be adjusted by stratification factors and baseline value if applicable. A sequential gate keeping procedure will be used to control the family-wise type I error rate in multiple testing of the primary and secondary efficacy endpoints. Summary of safety data will be based on the Safety Population. Safety parameters include adverse events, laboratory parameters, progression to AML, vital signs, ECG parameters, prior and concomitant medication use. **Data Safety Monitoring Board (DSMB)**: A Data Safety Monitoring Board (DSMB) will be established prior to the start of the DB portion of the study and will oversee the study on a regular and pre-defined basis. The role and function of the DSMB will be defined in the DSMB charter. Of particular note, the likely initial starting dose for the study is 2.0 mg/kg. This may be adjusted in agreement with the DSMB if supported by-data review.

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

2 BACKGROUND

The myelodysplastic syndromes (MDS) are clonal disorders of bone marrow characterized by ineffective hematopoiesis leading to peripheral blood cytopenias (anemia, neutropenia and thrombocytopenia), and an increased predisposition to developing acute myeloid leukemia (AML), especially in a high risk MDS category. The reported 3-year survival rate is 42% and the 5-year survival rate is 29% in MDS patients. Patients with higher risks for development of AML tend to have lower survival. The main features of MDS are peripheral blood cytopenias related to clonal stem cell disorder characterized by progressive ineffective hematopoiesis (Tefferi, 2009). Clonal evolution of abnormal hematopoietic stem cell is a multistep process involving genetic changes which can be identified by standard cytogenetic techniques and advanced molecular testing.

2.1 Introduction

2.1.1 Epidemiology of Myelodysplastic Syndrome

MDS affects at least 60,000 Americans. An incidence of 4.5 per 100,000 people was reported in 2006 by Surveillance, Epidemiology and End Results (SEER) and North American Association of Central Cancer Registries, Inc. (NAACCR) (Ma, 2007, Rollison, 2008). MDS is a disease of older adults, with a median age at diagnosis of approximately 71 years with a male predominance. With the exception of treatment-induced MDS (MDS that develops following chemotherapy or radiation treatment for another cancer), age of onset prior to 50 is uncommon in this disease. According to SEER data, only 4% of patients were reported to registries by physicians' offices (Rollison, 2008). Thus, MDS disease burden in the United States may be heavily underestimated.

2.1.2 Anemia Associated with MDS

Anemia is the most common clinical presentation in lower risk MDS, which results in prolonged transfusion requirements and risks related to red blood cell (RBC) transfusion itself, iron overload, and significant impairment of the quality of life in affected patients. The pathophysiology of anemia in MDS is complex, and involves ineffective erythropoiesis, dysregulated cytokine signaling, dysplastic features of hematopoietic progenitors and increased apoptosis of erythroid precursors, among other factors. The erythroid dysfunction in MDS often presents with fatigue and low hemoglobin level. Anemia in MDS become more symptomatic when Hb level becomes lower (i.e., below 9.0 g/dL) as erythroid dysfunction continues to decline, RBC transfusion may become necessary supportive treatment. Dependency on RBC transfusion has been associated with shorter life expectancy in patients with MDS. Anemia impacts across patients in all MDS categories of the International Prognostic Scoring System (IPSS-R) (Appendix G).

The disease burden of anemia in MDS is high. Severe anemia interferes with patients' quality of life and his/her ability to work as well as negatively impacting the function of other organ systems due to insufficient oxygen delivery to tissues. When RBC transfusion become necessary to sustain bodily functions, not only are the frequent trips to the hospital burdensome to the patient, the risk of transfusion-related infections can further threaten MDS patients some of whom may also have a primary neutropenia due to bone marrow dysfunction or secondary neutropenia associated with medications for the treatment of MDS; infection is the number one

cause of death in MDS patients. Additional risks with transfusion include transfusion reactions (risk accumulates with exposure to more antigens through transfusions) and the iron overload from cumulative transfusions may lead to additional organ complications, particularly in heart, liver and endocrine organs.

2.2 Current Treatment for MDS

The treatment options for lower risk MDS are limited. United States (US) Food and Drug Administration (FDA) approved treatments for MDS include the aza-nucleosides 5-azacitidine and decitabine, and are typically used for treating intermediate or higher IPSS risk patients. These hypomethylating agents (HMAs) can achieve a remission in a minority of the treated patients for a short duration of time before progression to AML, and are associated with significant levels of neutropenia and thrombocytopenia. Lenalidomide (Revlimid) is approved in the US and in the European Union for MDS patients with 5q(del) resulting in a 61% to 67% responder rate. Yet, 5q(del) represents only 7% to 15% of all MDS patients, and lenalidomide is not approved for MDS patients in many other parts of the world. Other than the high cost of treatment, lenalidomide is also associated with significant side effects such as neutropenia (55 to 75%) and thrombocytopenia (41% to 44%) (List, 2006). Stem cell transplantation (SCT) is the only treatment that has the potential to cure MDS, but it is only appropriate for young MDS patients who have high risk disease and have a HLA matched sibling/donor. No treatment has been shown to either delay disease progression or to prolong survival in lower risk MDS. Thus, the goal of therapy in these patients is to improve quality of life and reduce the transfusion burden.

There is no FDA or European Medicines Agency (EMA)-approved effective and safe pharmacologic treatment to treat anemia in lower risk MDS patients who are not suitable for lenalidomide or HMAs. To address anemia in lower risk MDS patients, erythropoiesis-stimulating agents (ESAs) are at times used off-label despite these agents are not approved for MDS patients by health authorities such as FDA or EMA. The guidelines of the National Comprehensive Cancer Network (NCCN) (version 1, 2016) recommends for symptomatic anemia, with serum EPO ≤500 mU/ml and ring sideroblasts <15% that either recombinant human erythropoietin (rh EPO) 40,000-60,000 units be given every 1-3 weeks subcutaneously or darbepoetin alfa 150-300 mg/weeks subcutaneously with the addition of granulocyte colony-stimulating factor (G-CSF) in patients with ring sideroblasts ≥15%. If a patient responds, the treatment should be continued and reduced to dose tolerance; however, there is no guidance on titration steps (up or down) nor on duration of treatment. This has resulted in a high degree of variability in clinical practice. The Clinical Practice Guidelines of the European Society for Medical Oncology (ESMO) indeed use weekly doses 30,000-80,000 units of EPO. Therefore, in the absence of a clear standard regimen of the available ESAs, this clinical trial will use placebo as the comparator not therefore require all patients to be exposed to subcutaneous treatment/placebo. Patients are allowed RBC transfusions during the study so that symptomatic anemia will be safely managed.

In order to achieve an erythroid response in MDS, the ESA dose used is three to five times higher than is required in anemia associated with chronic kidney disease (CKD). One of the potential reasons for this high ESA dose requirement has been suggested is that the inflammation seen in MDS may contribute to ESA-resistance. This inflammation is associated with hepcidin

elevation, functional iron deficiency on a progressively dysfunctional bone marrow. Patients who show an initial response to ESAs generally develop resistance to ESA in the course of their treatment, and will ultimately become dependent on blood transfusions as they stop responding to ESA. In addition to the extensively reported ESA dose-associated cardiovascular and thromboembolic risks in CKD patients, tumor progression risk is also reported in cancer patients with ESA use. The risk and benefit of ESA treatment for MDS patients is not well characterized due to a lack of adequate and well controlled studies with ESA in the MDS population.

The MDS classification system IPSS-R (Appendix G), takes into account the various prognostic variables of MDS including cytogenetics, bone marrow blasts, hemoglobin, platelets, and absolute neutrophil count. The risk categories in IPSS-R consists of Very Low Risk, Low Risk, Intermediate Risk, High Risk, and Very High Risk. "Lower risk" consisting of the majority of MDS patients, generally refers to very low (19% of MDS in US), low (38%), and a subset of intermediate (20%) depending on other risk factors in IPSS-R, and this category corresponds to the IPSS (International Prognostic Scoring System) categories of "low risk", and "intermediate-1 risk". "Higher risk" in IPSS-R includes some of intermediate (subset of 20%), high risk (13%), and very high risk (10%), and corresponds to the intermediate -2 and high risk in the IPSS.

MDS has a high disease burden without effective medical treatment. RBC transfusion is an unattractive last resort being used to support MDS patients with severe anemia. There is an urgent need to develop a novel, safe, and convenient therapy for addressing anemia in lower risk MDS.

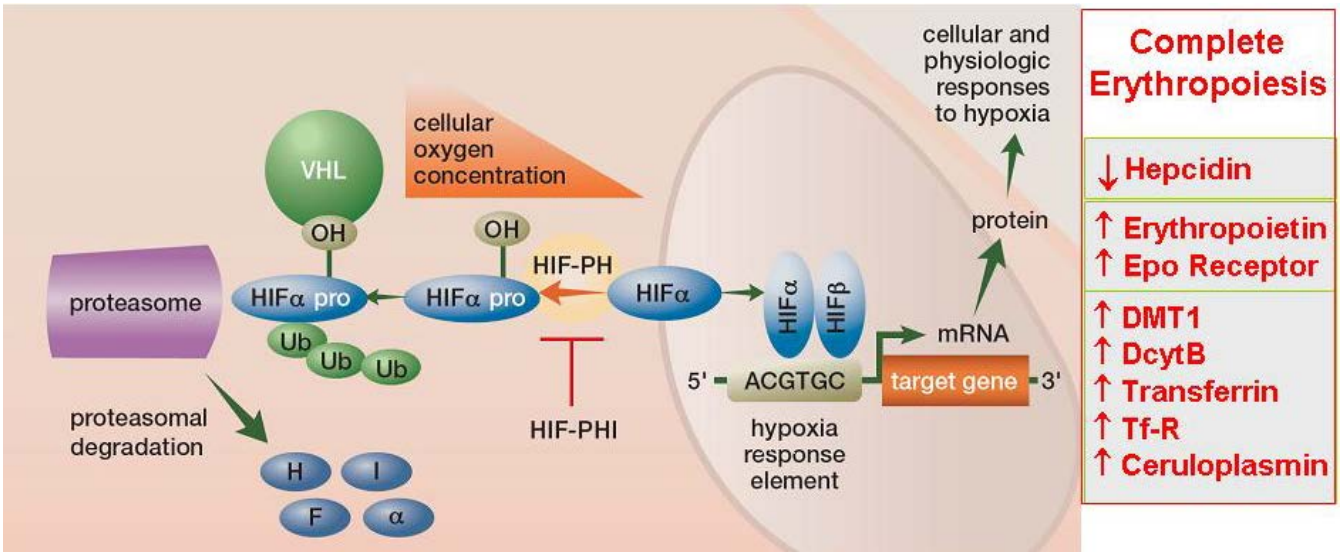
Roxadustat (FG-4592) is a new chemical entity belonging to a new pharmacological class of small molecule enzyme inhibitors (hypoxia inducible factor prolyl hydroxylase inhibitor, HIF-PHI). It is a potent and reversible inhibitor of the prolyl hydroxylase enzymes that regulate the stability of the hypoxia-inducible factor (HIF) for regulation of erythropoiesis. We currently propose to evaluate roxadustat for the treatment of anemia in very risk, low risk and intermediate risk with <5% bone marrow blasts in patients with low RBC transfusion burden (LTB).

2.3 Mechanism of Action of Roxadustat

Virtually all tissues depend on a sufficient supply of oxygen for survival. Lack of oxygen associated with hypoxic, ischemic, and anemic conditions triggers a series of homeostatic responses (Figure 1).

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

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



Abbreviations: DcytB = Duodenal cytochrome B; DMT1 = divalent metal transporter one; EPO = erythropoietin; HIF = hypoxia-inducible factor; HIF-PH = hypoxia-inducible factor prolyl hydroxylase; HIF PHI = hypoxia-inducible factor prolyl hydroxylase inhibitor; mRNA = messenger ribonucleic acid; Tf-R = Transferrin receptor; Ub = ubiquitin; VHL = Von Hippel–Lindau protein. Source: (Epstein, 2001).

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

Although HIF-α isoforms are constitutively produced, their accumulation under normoxic conditions is prevented by recruitment and binding by the von Hippel-Lindau (VHL) protein, which targets HIF-α isoforms for degradation through the ubiquitin-proteasome pathway. The molecular mechanism for oxygen-dependent degradation of HIF-α is based on the hydroxylation of specific proline residues, as catalyzed by a family of hypoxia-inducible factor prolyl hydroxylases (HIF-PHs) that utilize molecular oxygen as the substrate for hydroxylation. Thus, HIF-PH constitutes the body's main oxygen sensor by regulating the prevalence and activity of nuclear HIF protein. Under hypoxic conditions, HIF-PHs are inactive and lead to initiation of the HIF-responsive transcriptional cascade (Semenza, 1998, Wang, 1995).

Roxadustat is a potent and reversible hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) that transiently induces HIF stabilization and leads to a functional HIF transcriptional response that mimics the erythropoietic response associated with exposure of humans to intermittent hypoxia. HIF induces expression of not only EPO, but also the EPO receptor and proteins that promote iron absorption and recycling from the macrophage iron storage system (Peyssonnaux, 2008). Thus, roxadustat pharmacologically stimulates erythropoiesis via the HIF pathway and in a manner consistent with the body's normal homeostatic response to anemia, but under normoxic conditions. In contrast to the classical paradigm, suggesting that anemia in CKD patients is caused by the inability of these patients to produce EPO, results of a study of

roxadustat treatment of CKD patients not requiring dialysis (Study FGCL-SM4592-017) suggest that the kidneys and other sites of EPO production in this patient population retain the ability to produce sufficient EPO for robust erythropoiesis (Besarab, 2015).

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

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

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

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

2.4 Clinical Experience with Roxadustat

As of 07 September 2016, a total of 9,876 subjects, healthy and with CKD, have been enrolled in 31 completed studies (twenty-four Phase 1 and seven Phase 2) and in 12 ongoing studies (two Phase 2, 8 global Phase 3 studies, and two Phase 3 studies in China). In these studies, an estimated total of 5,912 subjects have received roxadustat, comprising 753 healthy subjects and an estimated 2,483 subjects with NDD CKD and 2,676 subjects DD CKD. Long term studies suggest durability of erythropoietic effect. There have been no safety concerns to date, inclusive

of negative thorough clinical study of QT/QTc interval prolongation which tested roxadustat dose up to 5 mg/kg in healthy volunteers.

Six completed FibroGen-sponsored phase 2 studies had 670 study patients with 545 patients exposed to roxadustat. Anemia correction and Hb maintenance with dose response were demonstrated across multiple studies with roxadustat in CKD patients on dialysis and those not on dialysis. The anemia correction response rates in anemic CKD patients not on dialysis (Studies FGCL-4592-041 and FGCL-4592-047) and those starting dialysis therapy (FGCL-4592-053) were >90%, enough though about half of the patients were not iron-replete at baseline, and that the severity of anemia were variable with baseline Hb that ranged between 6 to 10 g/dL (more details are provided in the Investigator Brochure). 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 and FGCL-4592-048).

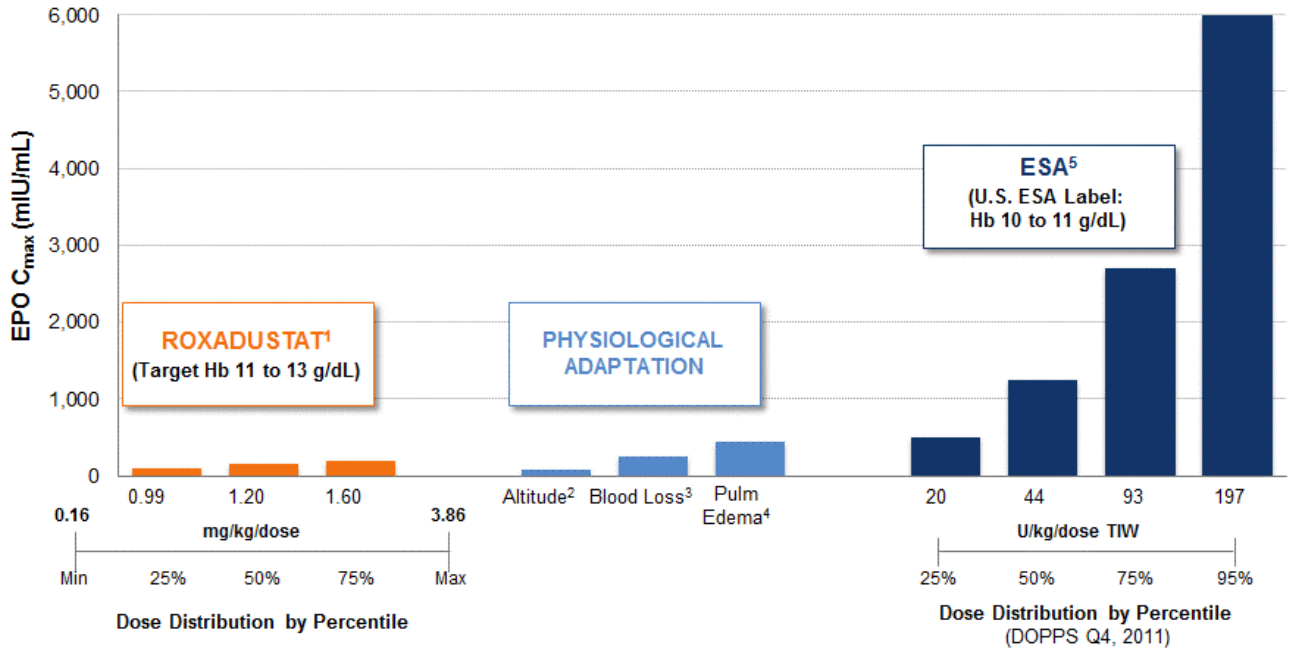
In CKD patients, the roxadustat dose requirement is not altered when baseline C-reactive protein level (CRP) is elevated, a measure of inflammation, which is suggestive of roxadustat's ability to overcome the dampening effect of inflammation on erythropoiesis. This is a challenge for ESA use for anemia in various patient population with chronic diseases. 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.

In addition to the subjects in the completed phase 1 and 2 studies, ongoing phase 3 studies have exposed >8,000 patients to roxadustat, some for over 2 years, and no safety signal with roxadustat has been identified.

2.4.1 Pharmacokinetics and Pharmacodynamics

Supraphysiologic 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 level 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. The Figure 2 depicts impact of environment on plasma EPO levels: with a range from 10 to 15 mIU/mL in healthy subjects 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 2) 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 2 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 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.

2.4.2 Experience with HIF-PHI in MDS, Rationale for Roxadustat in MDS Anemia, & Study Overview

FibroGen has conducted a study in ESA-refractory lower-risk MDS patients using FG-2216 which is a HIF-PHI with a similar mechanism of action to roxadustat, but its potency is only about a fifteenth that of roxadustat. In study FG-2216-014, 44 evaluable US ESA refractory lower-risk MDS patients (most of whom were transfusion-dependent) were dosed with FG-2216 with doses between 1250 mg to 2500 mg TIW for 16 weeks; some erythroid responses were observed. These doses of FG-2216 were comparable to roxadustat 70 mg to 150 mg, which is significantly below the maximum permitted roxadustat dose of 400 mg or 3.5 mg/kg (whichever is the lower).

Roxadustat is an orally active HIF-PHI with potent erythropoietic effects. Intermittent dosing of roxadustat results in transient activation of HIF, intermittent induction of endogenous, physiologic-range EPO, increased sensitivity to erythropoietin in the erythroid progenitor cells in the bone marrow, and dose-dependent erythropoiesis, suggests a coordinated mechanism of erythropoiesis that is different from ESA therapy, including beneficial effects on iron handling while overcoming barriers to erythropoiesis such as inflammation and iron availability as present

in many chronic disease conditions including MDS. The clinical data collected from >4000 subjects thus far suggest that roxadustat is generally safe and well tolerated in healthy adult subjects, and in dialysis-dependent and non dialysis-dependent CKD patients who have been enrolled and treated in completed and ongoing clinical studies.

Extensive clinical experience with roxadustat enables the design of this protocol in Lower-Risk MDS anemia. The study will comprise a 3:2 randomized (roxadustat:placebo) placebo controlled study with 160 lower risk patients (inclusive of anemic patients, with Hb ≤10 g/dL, in those who require RBC transfusion), with treatment duration of 52 weeks. The primary efficacy will be evaluated by the Sponsor after 28 weeks of DB treatment (Appendix A). The sites and investigators will remain blinded during the treatment period. The study will have 90% power to detect treatment difference of 35% vs 5% in roxadustat and placebo respectively for the primary endpoint of transfusion independence.

2.5 Roxadustat Dose Rationale

For the treatment of anemia in MDS patients, roxadustat will be administered orally three times per week (TIW) and titrated to achieve the target response. It is expected that patients will require a higher dose due to bone marrow dysfunction and this is supported by experience with the earlier agent FG-2216 as discussed in Section 2.4.2. The OL component will evaluate three cohorts (approximately 1.5 mg/kg, 2.0 mg/kg and 2.5 mg/kg) to optimize the starting dose for the DB component. After each 8 weeks on a dose level, the patient's response will be assessed and the study treatment will be titrated (pre-defined levels, Appendix C) to achieve transfusion independence. The study treatment can be down titrated at any time. Once the patient has achieved TI, the dose will be maintained as per Appendix D. The regimen is consistent with that of the roxadustat CKD clinical development program and utilizes tiered body weight. 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).

2.6 Risks/Benefits of Roxadustat Treatment

MDS has a high disease burden without effective medical treatment. RBC transfusion is an unattractive last resort being used to support MDS patients with severe anemia. There is an urgent need to develop an effective, safe, and convenient therapy for addressing anemia in lower risk MDS.

The primary benefit of roxadustat is the correction of anemia thus the reduction of RBC transfusions. This will result in the relief of the associated anemia signs and symptoms, the avoidance of the risks associated with RBC transfusions, and an improved quality of life for these elderly patients. Roxadustat is expected to overcome the inhibitory effect of inflammation of chronic disease on erythropoiesis, to improve erythropoietic progenitor cells' response to erythropoietin, to facilitate the mobilization of iron and ultimately lead to improved erythropoiesis.

A dose adjustment algorithm will be used during the Treatment Period to minimize transfusion burden with the primary goal of reaching transfusion independence, (Appendix C and Appendix D). The risk of excessive erythropoiesis (an increase in Hb of 2.0 g/dL at any time during the treatment period) will be mitigated by use of the dose adjustment algorithm. The

erythropoietic effects of roxadustat are reversible when treatment stops. Based on the clinical and nonclinical trial results to date, it is anticipated that orally administered roxadustat will be effective in the treatment of anemia in patients with MDS who have no approved treatment with an acceptable safety profile.

2.7 Objectives

2.7.1 Primary Objective

The primary objective of this study is to evaluate the efficacy of roxadustat in the treatment of anemia in patients with lower risk MDS who have a low burden of RBC transfusion.

2.7.2 Secondary Objectives

The secondary objectives in this study are to:

- Evaluate the safety of roxadustat
- Evaluate the impact of roxadustat on RBC transfusion requirements
- Evaluate pharmacokinetics (PK) and pharmacodynamics (PD) of roxadustat in MDS patients
- Evaluate effect of roxadustat on quality of life parameters

2.7.3 Open-Label Component Objective

- Optimize the starting dose for the DB component

2.8 Efficacy Endpoints

2.8.1 Primary Efficacy Endpoint*:*

The primary efficacy endpoint is the proportion of patients who achieved TI ≥56 consecutive days in the first 28 weeks of treatment.

2.8.2 Secondary Efficacy Endpoints

- Proportion of patients who achieved ≥50% reduction in number of RBC transfusion over any 8 weeks compared to their baseline
- Cumulative number of patient-exposure-week of TI
- Cumulative number of pRBC packs transfused
- Proportion of patients who achieved TI for ≥ 20 weeks (140 days)
- Mean change from baseline in Physical Function as measured by Patient Reported Outcomes Measurement Information System (PROMIS)
- Mean change from baseline in PROMIS Fatigue score.
- Mean change from baseline in EuroQol Quality of Life Five Dimensional Five Level Health Questionnaire (EQ-5D-5L) assessment

2.8.3 Exploratory Endpoints

- Duration of transfusion independence
- Proportion of patients who achieve a mean Hb increase of ≥1.0 g/dL and ≥1.5 g/dL (averaged over 8 weeks in those achieved TI) compared to pre-transfusion Hb at baseline

- Impact of baseline endogenous erythropoietin levels on roxadustat treatment response and dose requirement
- Effect on hepcidin and iron indices metabolism
- Effect on cholesterol and lipid parameters

2.9 Safety Assessments

Study-specific safety will be assessed by evaluating the following over 52 weeks:

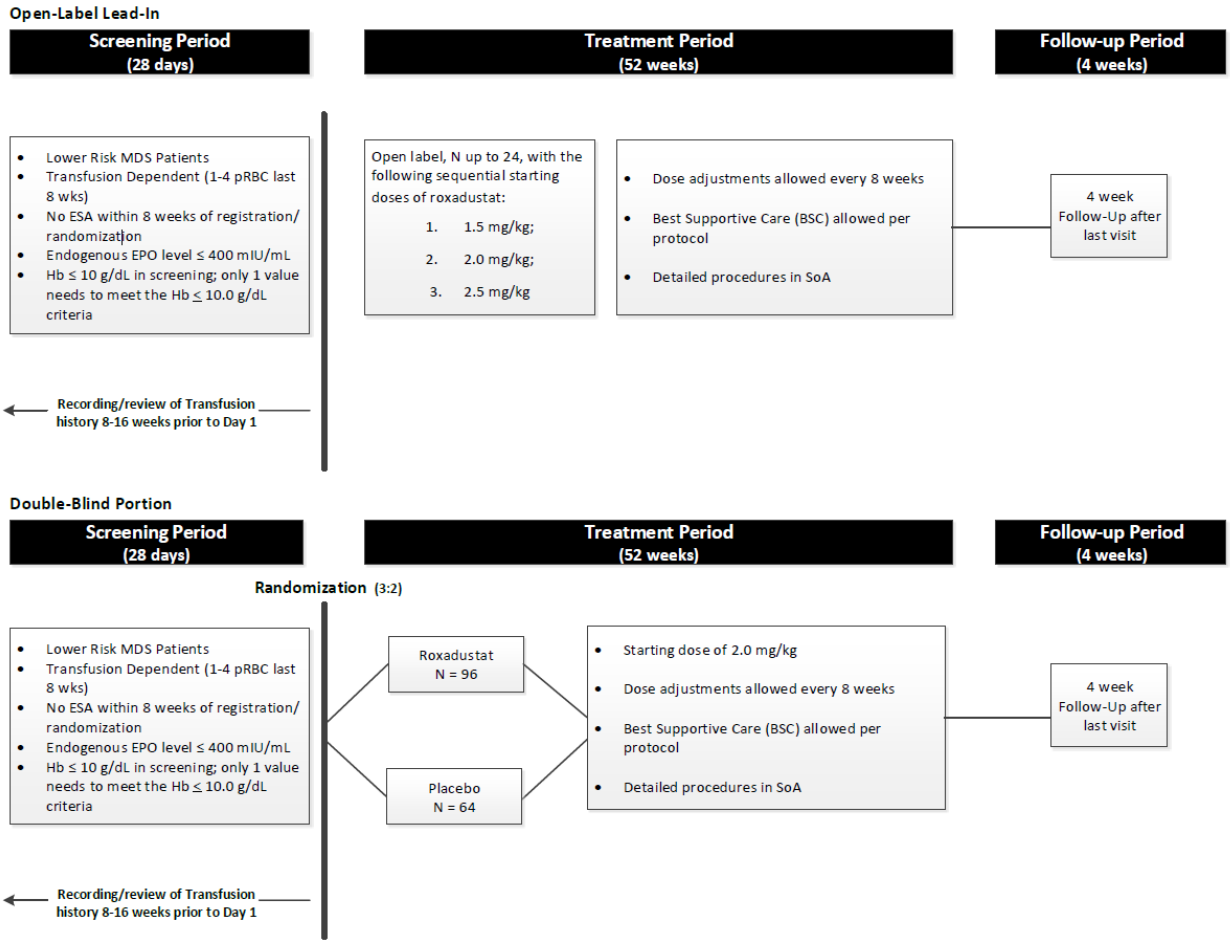
- AE and SAE reporting
- N (%) of patients with progression to AML
- Clinical laboratory measures, including Hb and LFTs (AST, ALT, TBili and ALP)
- Heart rate, blood pressure, and ECG changes (including changes from Baseline)
- Evaluation of PK/PD data

3 STUDY DESIGN

3.1 Description of the Study

The study design is illustrated in Figure 3 below:

Figure 3 Study Schemas



Up to 24 patients will be enrolled in sequential dose level cohorts prior to start of the DB component of the study. All patients will receive roxadustat in an OL manner. The first 8 patients will receive a starting dose of 1.5 mg/kg (Dose Level 1). The next 8 patients will receive a starting dose of 2.0 mg/kg (Dose Level 2). The last 8 patients will receive a starting dose of 2.5 mg/kg (Dose Level 3). Each patient's starting dose will be determined by their actual weight at the registration/randomization visit. The roxadustat dose per body weight are estimates only and the exact dose will be assigned per body weight ranges as shown in the body of the protocol.

The OL component is intended to optimize the starting dose for the subsequent double- blind component of the study in which 160 eligible lower risk MDS patients with LTB will be randomized 3:2 to roxadustat or matching placebo. It is anticipated that the starting dose level

will be level 2 (2.0 mg/kg) and the protocol is written to reflect this but if the OL data suggests a lower (1.5 mg/kg) or a higher (2.5 mg/kg) dose to be a more optimal starting dose, then this will be implemented accordingly.

Patients in the DB component of the study will be randomized with the following stratifications:

- Serum EPO level: either ≤200 mIU/mL OR >200 mIU/mL and ≤400 mIU/mL
- IPSS-R low risk / very low risk vs. intermediate risk group classification
- RBC transfusion burden: 1 pRBC/8-weeks over 16 consecutive weeks vs 2-4 pRBC/8-weeks

For the OL and the DB components, dose adjustments/escalations will occur every 8 weeks at pre-defined dose level increments, with the exception that the starting dose will be maintained if an erythroid response (defined as a 50% reduction in pRBC from baseline) is seen after the initial 8 weeks of dosing. A re-assessment will be done for these patients at week 12 and if transfusion independence (TI) is observed the dose will not be increased. If TI is NOT observed at this point, the dose will be increased by one dose level. See Appendix C for details on dosing and dose adjustment.

Once transfusion independence for at least 8 continuous weeks has been achieved and the "maintenance treatment period" starts, the study drug dose should follow guidance described in Appendix D.

When all the randomized patients complete 28 weeks of treatment or are discontinued from study medication before this time, the analysis of the primary and secondary efficacy endpoints will be performed. Only Sponsor personnel who are not directly involved with the study sites/patients will have access to the unblinded data. The blind will be maintained for study patients, PI, site staff and site monitoring personnel for the remainder of the study (to Week 52 plus a 4 week follow-up period).

The initial OL component with up to 24 patients who receive roxadustat may remain in the study up to 52 weeks of treatment based on investigator discretion, adequate safety, and impression of benefit. These patients will undergo all procedures as will the randomized patients with the exception of not completing the Health-related quality of life (HRQoL) questionnaires.

During the course of the study, visits and assessments will be performed as defined in the schedule of assessments (see Appendix A and Appendix B).

3.1.1 Screening Period

All screening procedures are to be completed within 28 days prior to Day 1 of Treatment, except for documentation of the following which can be obtained from patient medical records:

1. Lower risk MDS (IPSS-R very low risk, lower risk, or intermediate risk) must be documented prior to Day 1 of Treatment. There is no minimum time from diagnosis to registration/randomization except to allow for proper IPSS-R classification to be made, and to show transfusion dependence for patients in both portions of the study.
2. Results from bone marrow examination and cytogenetic analysis performed within 16 weeks prior to Day 1 of treatment can be used. The required bone marrow slides and report must be available for a centralized review at any time throughout the study.

3. Patients are deemed to have low RBC transfusion burden (LTB) if they received 1 to 4 pRBC documented transfusion within 8 weeks prior to registration/randomization. Patients with 1 pRBC/8-weeks must have a documented history of requiring 1pRBC/ 8-weeks in 2 consecutive periods of 8 weeks in the 16 weeks preceding registration/randomization. Pre-transfusion and post-transfusion Hb levels within 8 weeks prior to Day 1 of treatment will also be recorded. The percentage of patients requiring 1 pRBC transfusion at baseline will be capped at 30% for the DB portion of the study. For OL patients only, the requirement to demonstrate transfusion dependence can also be met by a PI starting this particular patient on pRBC transfusion during the screening period

All patients must meet all inclusion and have none of the exclusion criteria to be eligible to receive study medication.

3.1.2 Treatment Period

The treatment duration is 52 weeks.

3.1.3 Follow-Up Period

All patients who complete 52 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) will remain in the study through the entire 52 week study period. Patients will have a 4 week follow-up visit after stopping study medication and then be followed up at a reduced visit schedule of every 8 weeks after the final follow-up visit until the end of the study.

3.2 Replacement of Patients

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

3.3 Study Treatment

3.3.1 Dose and Schedule

Up to 24 patients will be enrolled in sequential dose level cohorts PRIOR to start of the DB component of the study. All patients will receive roxadustat in an OL manner. The first 8 patients will receive a starting dose of 1.5 mg/kg (Dose Level 1). The next 8 patients will receive a starting dose of 2.0 mg/kg (Dose Level 2). The last 8 patients will receive a starting dose of 2.5 mg/kg (Dose Level 3). All doses will be determined by actual patient weight on registration/randomization day.

The starting dosing table for the OL portion of the study is shown below.

Dose Level Group	Approximate Roxadustat Dose (mg/kg)	Patient Weight		
		45 to <70 kg	70 - 100 kg	> 100 kg
1	1.5	70 mg TIW	120 mg TIW	150 mg TIW
2	2.0	100 mg TIW	150 mg TIW	200 mg TIW
3	2.5	150 mg TIW	200 mg TIW	250 mg TIW

The OL is intended to optimize the starting dose for the subsequent DB component of the study in which 160 eligible lower risk MDS patients with LTB will be randomized 3:2 to roxadustat or matching placebo. It is anticipated that the starting dose level will be level 2 (2.0 mg/kg) and the protocol is written to reflect this but if the OL data identifies level 1 or 3 as a more optimal starting dose, then this will be implemented.

Patients in the DB component of the study will be randomized at an overall ratio of 3:2 to roxadustat or placebo with the following stratifications:

- Serum EPO level: either ≤200 mIU/mL OR >200 mIU/mL and ≤400 mIU/mL
- IPSS-R low risk / very low risk vs. intermediate risk group classification
- RBC transfusion burden: 1pRBC/8-weeks over 16 consecutive wks vs 2-4 pRBC/8wks

3.3.2 Dose Adjustment

There are two periods for the study drug dosing – the correction phase and the maintenance phase.

Correction phase: Dose adjustments/escalations will occur every 8 weeks at pre-defined dose level increments, with the exception that starting dose will be maintained if erythroid response (defined as a 50% reduction in pRBC from baseline) is seen after the initial 8 weeks of dosing. A re-assessment will be done for these patients at week 12 and if transfusion independence (TI) is observed the dose will not be increased. If TI is NOT observed at this point, the dose will be increased by one dose level (see Appendix C).

Maintenance Phase: Once transfusion independence for at least 8 continuous weeks (≥56 consecutive days) has been achieved and the "maintenance treatment period" starts, the study drug dose may be escalated or reduced in pre-defined levels as described in Appendix D.

During the course of the study, visits and assessments will be performed as defined in the schedule of assessments (see Appendix A).

Dose reductions can occur at any time per defined criteria (see Appendix C and Appendix D).

Dosing with study medication may be held (not given) for one single instance not to exceed 2 weeks. Please contact the medical monitor with any questions.

Given the complexities of the dose adjustment algorithm, and the need to take into consideration various clinical parameters, it is not considered a protocol deviation when study subjects are dosed based on their clinical circumstance, whether or not this is concordant with the roxadustat

dosing algorithm, unless it is related to "excessive hematopoiesis" or "Overdose" (prescribed 400 mg or > 3.5 mg/kg/dose).

3.4 Concomitant Medications, Procedures and Nondrug Therapies

3.4.1 Concomitant Medications

Concomitant medications are any prescription or over-the-counter preparations, including herbal products and "natural remedies," used by a patient while participating in this clinical study.

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

Use of herbal medicine during the study is not prohibited but strongly discouraged. All herbal and natural remedies should be reviewed by the investigator and if considered safe, may be allowed to continue at the same dose.

To avoid confounding effects on study endpoints, changes in administration of chronic concomitant medications should be minimized and done only if deemed necessary by the PI.

3.4.1.1 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.

3.4.1.2 Statins

When coadministered with roxadustat, in clinical pharmacolgical studies, hydroxymethylglutaryl coenzyme A reductase inhibitor (statin) exposure was increased 2- to 3-fold. Investigators should consider this interaction and local prescribing information when deciding on the appropriate statin dose for individual 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 1.

Table 1 Recommended Maximum Daily Dose of Statins

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

3.4.2 Supplemental Iron Use

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

3.4.3 Best Supportive Care

Best supportive care including RBC transfusion is permitted to ensure patient's safety. The PI and site staff will utilize their own institutional criteria for the determination of when to transfuse a patient. Use of any ESA (epoetin alfa, epoetin beta, darbepoetin or others) is not permitted (see Appendix I) and patients who receive an ESA will be discontinued from further treatment with study medication.

3.4.4 Emergency Procedure (Therapeutic Phlebotomy)

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

3.4.5 Prohibited Medications/Therapies/Substances

The following medications/therapies are prohibited from 8 weeks prior to screening through to the End of Treatment visit except for ESAs which are prohibited for 8 weeks prior to Week 1 Day 1 registration/randomization visit and at any time during the study (see first bullet below regarding ESAs)

- Any use of ESAs (erythropoietin stimulating agents) 8 weeks prior to Week 1 Day 1 registration/randomization, such as epoetin alfa, epoetin beta, darbepoetin, etc. (see Appendix I). Patients who receive an ESA during the study will be discontinued from further treatment with study medication. Patients who discontinue study medication early (for any reason) will remain in the study through the 52 week study period. Patients will have a 4 week follow-up visit after stopping study medication and then be followed up at a reduced visit schedule of every 8 weeks until the end of the study.
- Androgens
- IV iron (but oral iron is allowed)
- Agents intended to treat MDS, e.g., azacitidine, decitabine, thalidomide, or lenalidomide
- Granulocyte colony stimulating factors (G-CSF). Exception is that G-CSF can be used per package insert/local prescribing directions to treat infections and/or pancytopenia, but NOT as prophylaxis.
- Dapsone
- Acetaminophen >2 g/day for more than 7 days
- Investigational agents such as luspatercept, etc.

3.4.6 Contraception

Female patients of childbearing potential, if not practicing complete sexual abstinence, must agree to an acceptable method of contraception. Male patients (nonsurgically sterile; i.e., no vasectomy) with female partners of childbearing potential who are not on birth control must agree to use a barrier method of contraception (e.g., condom) or the female partner must agree to use contraception as described above unless practicing complete sexual abstinence.

Patients must agree to practice above contraceptive methods, as applicable, for the entire duration of the study, from registration/randomization through the EOT visit. It is highly recommended that they continue to practice the contraceptive methods for 12 weeks following

the last dose of study treatment. 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 (Section 7.3.6).

3.5 Safety Monitoring Plan

Safety will be assessed throughout the study. A complete baseline profile of each patient will be established through demographics, medical history, clinical laboratory values, vital signs, physical examination (PE), and electrocardiogram (ECG). During the course of the study, vital signs and laboratory tests will be performed at regular intervals as described in schedule of assessments (Appendix A and Appendix B).

Blood pressure (BP) and heart rate (HR) should be assessed according to the guidelines described in Appendix N.

A physical exam (PE) will be conducted during Screening, Day 1, Week 28, EOT and at the 4 Week post-EOT visit.

Any significant findings prior to administration of study drug will be considered as baseline conditions and will be captured as baseline medical history. Any clinically significant (CS) changes from baseline will be monitored throughout the study and appropriate interventions will be taken accordingly. Clinical laboratory tests may be assessed at additional times on unscheduled visits for safety reasons. Liver function abnormalities will be monitored according to drug-induced liver injury (DILI) guidance (Appendix H).

All adverse events (AEs), serious AEs (SAEs), and ongoing concomitant medication usage will be monitored and recorded throughout the study. SAE reports will be evaluated individually to assess the impact of the event, if any, on the overall safety of the product and on the study itself. Cumulative AEs will be monitored throughout the study. SAEs and AEs will be followed until resolved, deemed stable, or until the patient's 4-week post EOT visit. See Section 7 for details on AE and SAE reporting.

3.6 Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) will be established prior to the start of the DB portion of the study and will oversee the study on a regular and pre-defined basis. The role and function of the DSMB will be defined in the DSMB charter. Of particular note, the likely initial starting roxadustat dose for the DB portion of the study is 2.0 mg/kg. This may be adjusted in agreement with the DSMB if supported by data review.

4 STUDY ENROLLMENT AND WITHDRAWAL

4.1 Inclusion Criteria

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

1. Diagnosis of primary MDS (confirmed by bone marrow aspirate and biopsy prior to treatment Day 1), classified by the IPSS-R as very low, low, or intermediate risk with <5% bone marrow blasts. There is no minimum time from diagnosis to registration/randomization except to allow for proper IPSS-R classification to be made, and to show transfusion dependence for patients in both portions of the study.
2. RBC transfusion requirement of either:
    a. 2 to 4 pRBC over the 8-weeks prior to registration/randomization,

    OR

    b. 1 pRBC during the 8-weeks prior to registration/randomization: Patients with 1 pRBC must have a documented history of requiring 1 pRBC/8-weeks in 2 consecutive periods of 8 weeks in the 16 weeks preceding registration/randomization
    c. The PI and site staff will utilize their own institutional criteria for the determination of when to transfuse a patient.
    d. **Open-Label patients only**, the requirement to demonstrate transfusion dependence can also be met by a PI starting this particular patient on pRBC transfusion during the screening period.
3. There is no restriction on prior use of recombinant erythropoietins or analogues (erythropoiesis-stimulating agents (ESAs)), except that the patient must not have received any ESA within the 8 weeks prior to Day 1 registration/randomization. ESAs include but are not limited to any recombinant human erythropoietin and other drugs listed in Appendix I.
4. Hb ≤10.0 g/dL during Screening period. Hb values are obtained at Screening Visit 1 and 2; only 1 value needs to meet the Hb ≤ 10.0 g/dL criteria. These values must be the Central Laboratory values. A third value may be obtained if necessary.
5. Age ≥18 years
6. Body weight ≥45 kg
7. ECOG performance status of 0, 1 or 2 at last screen visit (see Appendix F)
8. Must be capable of giving written informed consent

4.2 Exclusion Criteria

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

1. Diagnosis of secondary MDS associated with prior chemotherapy, extensive radiation therapy (>25% of bone marrow reserve), and or/other significant chemical or radiation exposure
2. Previous diagnosis of IPSS-R high risk or very high risk MDS (see Appendix G)

3. Planned myeloablative or craniospinal radiation during the study
4. Prior bone marrow or stem-cell transplantation (SCT)
5. Significant myelofibrosis (>2+ fibrosis)
6. MDS associated with 5q(del) cytogenetic abnormality
7. Screen serum erythropoietin level > 400 mIU/mL
8. Alanine aminotransferase (ALT) > 3 x ULN, **OR** aspartate aminotransferase (AST) > 3 × ULN **OR** TBili > 1.5 × ULN (see Appendix H)
9. Azacitidine, decitabine, thalidomide, lenalidomide, G-CSF, or luspatercept, or any investigational drugs within 8-weeks prior to Day 1 treatment or plans to use any of these medications during the course of clinical trial participation
10. Anticipated use of dapsone at any dose amount or chronic use of acetaminophen or paracetamol >2.0 g/day during the study for more than 7 days
11. Clinically significant anemia, as determined by the investigator, due to non-MDS etiologies such as iron deficiency, vitamin B_{12} or folate deficiency, autoimmune or hereditary hemolysis or anemia or hemorrhage or hereditary anemia such as sickle cell anemia or thalassemia
12. Active infection(s) requiring systemic antibiotic therapy
13. Cockroft-Gault calculated estimated glomerular filtration rate (eGFR) <30 mL/min
14. Thromboembolic event such as DVT, pulmonary embolism, myocardial infarction, stroke, or TIA, within previous 6 months
15. Current condition requiring anticoagulant, e.g., warfarin or enoxaparin, a factor Xa inhibitor such as rivaroxaban or apixaban, or a direct thrombin inhibitor such as dabigatran. Chronic use of low-dose aspirin is allowed.
16. Significant heart disease, including 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
17. Clinically significant or uncontrolled ongoing inflammatory/autoimmune disease (e.g., rheumatoid arthritis, Crohn's disease, celiac disease, etc.)
18. History of significant liver disease or active liver disease
19. Major surgery planned during the treatment period
20. Known, active or chronic gastrointestinal bleeding
21. Known human immunodeficiency virus (HIV), hepatitis B or hepatitis C infection
22. 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
23. History of leukemia or other active malignancy except localized and non-metastatic squamous or basal cell carcinoma of the skin, or cervical intraepithelial neoplasm; patients with a history of cured malignancy with no evidence of recurrence for at least 3 years are eligible

24. Previous recipient of roxadustat or another hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI)
25. Pregnant or breastfeeding females

4.3 Treatment Discontinuation

Patients who discontinue study medication early (for any reason) will remain in the study through the 52 week study period. Patients will have a 4 week follow-up visit after stopping study medication and then be followed up at a reduced visit schedule of every 8 weeks until the end of the study.

Patients will be discontinued from treatment for the following reasons (below and Appendix H and Appendix O):

a. Disease progression: Diagnosis of AML during the study

b. Liver Function: Discontinuation of treatment will occur 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 international normalized ration (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%)

A patient who decides to discontinue treatment with study medication will always be asked about the reason(s) for discontinuation and the presence of AEs (if any). These data will be ascertained and documented by the investigator and recorded in the electronic case report forms (eCRF) as appropriate. The patient should return all study medications.

Reasons for permanent discontinuation of treatment with study medication:

- Patient's decision (subject no longer wants to continue study medication (i.e., withdrawal of consent)
- Investigator's decision that it is in the best interest of the patient to be withdrawn from the study
- AEs (including SAEs)
- Significant noncompliance with study procedures, as determined by Investigator or Sponsor
- Lack of efficacy
- Treatment with ESAs
- Patient is lost to follow-up
- Site terminated by the Sponsor
- Pregnancy
- Death

4.4 Replacement of Patients

Patients will not be replaced for this study.

4.5 Study Termination

This trial can be terminated by the Sponsor at any time for any reason.

4.6 Blinding

For the DB component of the study, the Investigator, study site staff, subject and the Sponsor and designees, are blinded to study drug assignment, but not to the dose. Additionally, all efforts should be made to keep subjects blinded to study Hb values.

4.6.1 Maintenance of Blinding

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

4.6.2 Planned and Unplanned Unblinding of Treatment Assignment

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

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

5 INVESTIGATIONAL PRODUCT

5.1 Formulation

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). Placebo tablets are similar to the roxadustat tablets except for the absence of active roxadustat.

5.2 Storage

Roxadustat tablets should be stored at room temperature between 15°C and 30°C (59ºF to 86ºF).

Placebo should be stored under the same conditions.

All study drugs should be stored in a securely locked area to which access is limited to appropriately authorized study personnel.

5.3 Study Drug Handling and Disposal

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

5.4 Route of Administration and Dose

5.4.1 Roxadustat/Placebo

All patients will take doses TIW for the entire duration of the study. Roxadustat/placebo 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 /placebo 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 at the same time of day. Roxadustat/placebo can be taken with water and with or without food.

5.5 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.

6 STUDY PROCEDURES

During study visits, all assessments including laboratory assessments and physical examinations must be completed prior to registration/randomization and first dose. Quality of life (QoL assessments (Appendix E) should be administered approximately at the same time of the day throughout the entire study. Laboratory tests are tabulated in Appendix K. Blood pressure and heart rate (HR) should be assessed according to the guidelines described in Appendix N.

6.1 Screening Period

After signing the Informed Consent, patients will enter the Screening Period. AEs and SAEs will be recorded in the medical record as of the signing of consent date. SAEs will be reported to FibroGen. All screening procedures are to be completed within 28 days prior to Day 1 except for documentation of the following which can be obtained from patients' medical records:

1. Lower risk MDS (IPSS-R very low risk, lower risk, or intermediate risk) prior to Day 1 of treatment. There is no minimum time from diagnosis to registration/randomization except to allow for proper IPSS-R classification to be made, and to show transfusion dependence for patients in both portions of the study.
2. Results from bone marrow examination and cytogenetic analysis performed within 16 weeks prior to registration/randomization can be used. The required bone marrow slides and report must be readily available for a centralized review at any time throughout the study.
3. Patients are deemed to have low RBC transfusion burden (LTB) if they received 1 to 4 documented pRBC transfusions within 8 weeks prior to randomization. Patients with 1 pRBC/8-weeks must have a documented history of requiring 1 pRBC/8-weeks in 2 consecutive periods of 8 weeks in the 16 weeks preceding registration/ randomization. Pre-transfusion and post-transfusion Hb levels within 8 weeks prior to Day 1 of treatment will also be recorded. The percentage of patients having 1pRBC transfusion at baseline will be capped at 30% for the DB portion of the study. For Open-Label patients only, the requirement to demonstrate transfusion dependence can also be met by a PI starting this particular patient on pRBC transfusion during the screening period.
4. RBC transfusions over the 16 weeks prior to Day 1 will be recorded for all patients. Pre-transfusion and post-transfusion Hb levels within 8 weeks prior to randomization will also be recorded. The PI and site staff will utilize their own institutional criteria for the determination of when to transfuse a patient.

6.1.1 Screening 1

- Signed written informed consent
- Inclusion/Exclusion criteria verification (eligibility review)
- Demographics and medical history (including bone marrow biopsy)
- ECG
- ECOG Score
- Physical Exam

- Weight
- Vital signs (BP, HR, respiratory rate [RR], and temperature [Temp])
- Laboratory tests (Appendix K):
    - Complete blood count (CBC) with Hb level and white blood cell (WBC) differential
    - Serum chemistries (sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, magnesium, phosphorus, lactate dehydrogenase (LDH), albumin)
    - Liver function tests (LFTs) – AST, ALT, total bilirubin, alkaline phosphatase
    - Iron Biomarkers: serum iron, ferritin, total iron-binding capacity (TIBC), unsaturated iron-binding capacity (UIBC), transferrin saturation (TSAT)
    - Reticulocyte count and hemoglobin in reticulocytes (CHr)
    - Vitamin B_{12} and folate
    - Enzyme-linked immunosorbent assay (ELISA) for HIV
    - Hepatitis B surface antigen (HBsAg)
    - Anti-hepatitis C virus (HCV) antibody
    - Prothrombin time (PT) and partial thromboplastin time (PTT)
    - Hepcidin level
    - Serum pregnancy (for females of childbearing capability)
    - Serum endogenous erythropoietin level
- Review and record concomitant medications
- Review and record transfusions (for 16 weeks prior to anticipated first dose date)
- Review and record procedures and nondrug therapies
- Review and record AEs, if any (capture the event under medical history, if applicable)

6.1.2 Screening 2

Hemoglobin values must be obtained at least 4 days apart and the screening 2 visit must be ≥4 days apart from the screening 1 visit.

- ECOG
- CBC with Hb level and WBC differential
- Liver function tests (LFTs)
- Review and record concomitant medications
- Review and record transfusions since Screen 1 visit
- Review and record procedures and nondrug therapies
- Review and record AEs, if any (capture the event under medical history, if applicable)

6.1.3 Additional Screening Assessments

A patient who fails screening may be rescreened, only upon approval from the Medical Monitor.

For all screen failures, the reason(s) will be documented.

6.2 Registration (OL) and Randomization (DB)

For the OL component, eligible patients will be sequentially assigned to the cohorts, starting with 1.5mg/kg for the first 8 patients, then 2.0mg/kg for the next 8 patients and at 2.5mg/kg for the last 8 patients.

For the DB component eligible patients will be randomized based on stratification factors to receive roxadustat or placebo. Randomization must take place prior to administration of study drug.

6.3 Treatment Period

Patients will attend weekly study visits for the first four weeks, from Day 1, Week 1 to Week 4, then from Weeks 5 to Week 28 study visits will be performed every two weeks. At Week 27 an additional CBC and Hb will be collected.

When all the randomized patients complete 28 weeks of treatment or have study medication discontinued before this time, the analysis of the primary efficacy and secondary endpoints will be performed. Only sponsor personnel who are not directly involved with the study sites/patients will have access to the unblinded data. The blind will be maintained for study patients, PI, site staff and site monitoring personnel for the remainder of the study (to Week 52 plus a 4 week follow-up period). From Week 31 to Week 52, study visits will be performed every 4 weeks. Patients who discontinue treatment early (for any reason) will remain in the study through the 52 week study period, but at reduced visit schedule of every 8 weeks with the exception of a follow-up visit 4 weeks after the last dose of study medication.

6.3.1 Study Procedures and Assessments by Visit

6.3.1.1 Study Procedures and Assessments to be Done at All Study Visits

The following will be done at ALL study visits within the Treatment and Follow-Up Periods:

- Recording of transfusions
- Central CBC with Hb level and WBC differential
- Local hemoglobin level (hemocue device is encouraged but not required)
- Review and record AEs
- Review and record concomitant medications, procedures and non-drug therapies
- Review hemoglobin level for any dose adjustments that are deemed necessary (Appendix C and Appendix D)
- Ensure patient dosing compliance

Local laboratory testing of Hb for dose adjustment decisions will be done at the Local level – use of the Hemocue device is encouraged but not required. Central laboratory values of Hb will be used for all data analysis purposes

6.3.1.2 Additional Study Procedures/Assessments and Blood Sampling by Visit

Table 2 below lists additional study procedures/assessments and blood sampling by visit for the 52-week Treatment Period, EOT and Post-EOT.

All blood samples must be drawn prior to dose unless otherwise noted (e.g. certain PK draws).

Table 2 Additional Study Procedures/Assessments and Blood Sampling by Visit for the 52-Week Treatment Period, EOT and Post-EOT (Appendices A, B, K)

Study Visit	Procedures and Assessments	Blood Samples
Day 1 (Week 1)	• Inclusion/Exclusion criteria verification/review (including documentation of MDS) • ECOG score • Weight • Vital signs (BP, HR, RR, and Temp) immediately prior to the time of the PK sampling • Health-related quality of life (HRQoL) assessments • Review and record baseline conditions, AEs, if any (capture the event under medical history, if applicable) • Register/Randomize patient (dose confirmation) • Dispense study drug • Dose patient (first dose should be given at the site)	• Serum chemistries • Serum lipid panel • LFTs • Iron biomarkers • PT and PTT • Hepcidin • C-reactive protein • Serum pregnancy (for females of childbearing capability) • Endogenous serum EPO level • PK samples 1-3 and 3-5 hours after dosing • CBC (central) and Local Hb
Week 2		• CBC (central) and Local Hb
Week 3	• Dispense study drug	• LFTs • CBC (central) and Local Hb
Week 4		• CBC (central) and Local Hb
Week 5	• Vital signs (BP, HR, RR, and Temp) at the time of PK sampling • ECOG score • Dispense study drug	• Serum chemistries • Serum lipid panel • LFTs • Iron biomarkers • Hepcidin • Endogenous serum EPO level • Reticulocytes & CHr • PK sample 4-6 hours after dosing • CBC (central) and Local Hb
Week 7	• Dispense study drug	• CBC (central) and Local Hb
Week 9	• Dose adjustment review • Vital signs (BP, HR, RR, and Temp) • Dispense study drug • Health-related quality of life HRQoL	• CBC (central) and Local Hb • Serum chemistries • LFTs • Iron biomarkers

Table 2 Additional Study Procedures/Assessments and Blood Sampling by Visit for the 52-Week Treatment Period, EOT and Post-EOT (Appendices A, B, K)

Study Visit	Procedures and Assessments	Blood Samples
	assessments • Assess erythroid response	• Reticulocytes & CHr
Week 11	• Dispense study drug	• CBC (central) and Local Hb
Week 13	• Dose adjustment review • Vital signs (BP, HR, RR, and Temp) • Point-of-care urine pregnancy test • ECOG score • Dispense study drug	• CBC (central) and Local Hb • Serum chemistries • LFTs • Iron biomarkers • Hepcidin • Reticulocytes & CHr
Week 15	• Dispense study drug	• CBC (central) and Local Hb
Week 17	• Dose adjustment review • Vital signs (BP, HR, RR, and Temp) • Dispense study drug • Health-related quality of life HRQoL assessments • ECOG score	• CBC (central) and Local Hb • Serum chemistries • LFTs • Iron biomarkers • Reticulocytes & CHr
Week 19	• Dispense study drug	• CBC (central) and Local Hb
Week 21	• Dose adjustment review • Vital signs (BP, HR, RR, and Temp) at time of PK sampling • Dispense study drug	• CBC (central) and Local Hb • Serum chemistries • Serum lipid panel • LFTs • Iron biomarkers • Hepcidin • Endogenous serum EPO level • Reticulocytes & CHr • PK sample 8-10 hours after dosing
Week 23	• Dispense study drug	• CBC (central) and Local Hb
Week 25	• Dose adjustment review • Vital signs (BP, HR, RR, and Temp) at the time of the PK sampling • Point-of-care urine pregnancy test • Dispense study drug • ECOG	• CBC (central) and Local Hb • Serum chemistries • LFTs • Iron biomarkers • Hepcidin • Endogenous serum EPO level • Reticulocytes & CHr • PK samples 0-2 hours before dosing and 2-3 hours after dosing
Week 27	• Dispense study drug	• CBC (central) and Local Hb

Table 2 Additional Study Procedures/Assessments and Blood Sampling by Visit for the 52-Week Treatment Period, EOT and Post-EOT (Appendices A, B, K)

Study Visit	Procedures and Assessments	Blood Samples
Week 28	• Physical Exam • ECG • Weight • Vital signs (BP, HR, RR, and Temp) • Health-related quality of life (HRQoL) assessments • ECOG	• CBC (central) and Local Hb • Serum chemistries • Serum lipid panel • LFTs • Iron biomarkers • B_{12} and folate • PT and PTT • Hepcidin • C-reactive protein • Endogenous serum EPO level • Reticulocytes & CHr
Week 31	• Dose Adjustment review • Dispense study drug	• CBC (central) and Local Hb
Week 35	• Dose adjustment review • Dispense study drug	• CBC (central) and Local Hb
Week 39	• Vital signs (BP, HR, RR, and Temp) • Point-of-care urine pregnancy test • Dispense study drug	• Serum chemistries • Serum lipid panel • LFTs • Hepcidin • Iron biomarkers • Reticulocytes & CHr • CBC (central) and Local Hb • Endogenous serum EPO level
Week 43	• Dose adjustment review • Dispense study drug	• CBC (central) and Local Hb
Week 47	• Dispense study drug	• CBC (central) and Local Hb
Week 52/EOT	• Bone marrow aspirate and biopsy • Physical Exam • Vital signs (BP, HR, RR, and Temp) • ECG • ECOG score • Health-related quality of life HRQoL assessments	• CBC (central) and Local Hb • Serum chemistries • LFTs • Iron biomarkers • Hepcidin • Endogenous serum EPO level • PT, PTT • Serum lipid panel • B_{12} and folate • C-reactive protein • Reticulocytes & CHr • Serum pregnancy (for females of childbearing capability)
4 Weeks Post-EOT	• Physical Exam • ECOG score • Vital signs (BP, HR, RR, and Temp) • Health-related quality of life (HRQoL)	• CBC (central) and Local Hb • Serum chemistries • LFTs • Iron biomarkers

Table 2 Additional Study Procedures/Assessments and Blood Sampling by Visit for the 52-Week Treatment Period, EOT and Post-EOT (Appendices A, B, K)

Study Visit	Procedures and Assessments	Blood Samples
	assessments • ECG	• Hepcidin • Endogenous serum EPO level • PT, PTT • Serum lipid panel • B_{12} and folate • C-reactive protein • Reticulocytes & CHr • Serum pregnancy (for females of childbearing capability)
If Early Termination, every 8 weeks assessment from 4 Weeks Post-EOT visit. Last visit at Week 52 from first dose.	• Vital signs (BP, HR, RR, and Temp)	• CBC (central) and Local Hb • Serum chemistries • LFTs • Iron biomarkers • Hepcidin • Endogenous serum EPO level

6.4 Follow-up Period after EOT or Early Termination of study medication

Patients who discontinue study medication early (before week 52) will have an EOT visit and then a 4 week follow-up visit. They will then be followed up at a reduced visit schedule of every 8 weeks until the end of the study (see Table 2).

6.5 Missed Visits

Every attempt should be made to complete all study visits within the visit window as outlined in the Schedule of Assessments (Weeks 1-5 (± 1 day), Weeks 7-52 ± 2 days). Appendix A

6.6 Unscheduled Visits

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

6.7 Laboratory Assessments

Central laboratory results should be reviewed by the Investigator as it is received. Any abnormalities must be evaluated in clinical context and the investigator should determine if it is clinically significant. Patient management is dependent upon close review of the laboratory data.

6.8 Local Hb Level

Hb levels will also be done at specified visits. Use of a HemoCue device is encouraged but not required. These values will be recorded in the CRF and used for dose adjustment assessments only.

6.9 Central Laboratory

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

Unscheduled and repeat laboratory tests will also be performed by the central laboratory. However, if the turnaround time from the central laboratory is not sufficiently rapid for clinical management of the patient, local laboratory (i.e., Stat Lab) test results may be used to make the necessary clinical judgments. Stat lab is to be used only for urgent lab test that are needed for immediate decision making related to the protocol management of adverse events as determined by the Investigator. In all cases, a central laboratory specimen would also be drawn at the same time. A central laboratory manual with instructions on specimen collection, processing, storing, and shipping to the central laboratory will be provided to all participating sites.

Laboratory tests for this study are listed in Appendix K.

6.10 Electrocardiogram

Local 12-lead ECGs will be performed on all patients at screening, Week 28, end of treatment and the 4 week follow-up visit as described in the Schedule of Assessments. The ECG should be taken after 5 minutes in the supine position. Any abnormalities must be evaluated in clinical context (based on patient's medical history and concomitant medication) and the investigator should determine if it is clinically significant. Clinically significant abnormalities should be reported as an AE. ECG recordings will be kept as source documents. Abnormal ECG findings prior to administration of study drug on Day 1 will be considered baseline conditions.

6.11 Health Related Quality of Life Questionnaires

The main goal of therapy in lower risk MDS patients is to provide symptom control related to anemia and also improve HRQoL.

Moreover, in Phase 2 studies in patients with NDD-CKD (Study FGCL-4592-041) and DD-CKD (Study FGCL-4592-053) in which Hb correction was an objective, patients were administered patient-reported outcome (PRO) questionnaires to assess the effect of roxadustat on HRQoL. In general, significant improvements from baseline were observed in the anemia and physical well-being subscales of the Functional Assessment of Cancer Therapy-Anemia (FACT-An) questionnaire (FACIT, 2014), and in the vitality, mental, and physical component subscales of the Short Form-36 (SF-36) questionnaire (Ware, 1993). The improvements were more pronounced in patients with the lowest scores at baseline. The impact of roxadustat on the remaining PRO subscores and questionnaires was less clear in these studies, over this duration.

Based on this experience, this protocol prospectively includes HRQoL instruments to evaluate the impact of roxadustat on MDS patients' HRQoL. Our goal is to demonstrate improvements in HRQoL utilizing specific items and domains from instruments most appropriate for the targeted population. All these instruments will be performed with the patients as the rater, including:

1. Patient-Reported Outcomes Measurement Information System (PROMIS®; Cella, 2007; Cella, 2010)

2. European Quality of Life Five Dimension, Five Level Health Questionnaire (EQ-5D-5L, Rabin, 2001)

The rationale for each of the PRO items and domains selected includes consideration of the applicable concepts to be evaluated and context of use for this study.

Specific symptoms that are most important to the MDS population are fatigue/tiredness. Currently, there are no existing perfect measures to capture these symptoms.

PROMIS provides clinicians and researchers access to reliable, valid, and flexible measures of health status that assess physical, mental, and social well–being from the patient perspective. PROMIS measures are standardized, allowing for assessment of many patient-reported outcome domains, including pain, fatigue, emotional distress, physical functioning and social role participation, based on common metrics that allow for comparisons across domains, across chronic diseases, and with the general population. Further, PROMIS tools allow for computer adaptive testing, efficiently achieving precise measurement of health status domains with few items. There are PROMIS measures for both adults and children. PROMIS was established in 2004 with funding from the National Institutes of Health (NIH) as one of the initiatives of the NIH Roadmap for Medical Research.

EQ-5D-5L is a standardized instrument for measuring generic health status. The health status measured with EQ-5D-5L is used for estimating preference weight for that health status, then by combining the weight with time, quality-adjusted life year (QALY) can be computed. QALYs gained is used as an outcome in cost-utility analysis which is a type of economic evaluation that compares the benefit and cost of health care programs or interventions. Many countries generated a value set (preference weights) of their own population and have used it for estimating QALY to make decisions in resource allocation. There are currently 171 language versions of EQ-5D-5L questionnaire available. EQ-5D-5L is one of the most commonly used generic health status measurement, and its good validity and reliability have been reported in various health conditions.

Importantly, PROMIS is a validated instrument for the MDS population (Abel, 2014), and so is EQ-5D-5L (Efficace, 2015). Please also refer to Appendix E.

7 SAFETY

7.1 Background

All AEs reported spontaneously during the course of the study will be recorded. The investigator must immediately (within 24 hours of awareness) report to the Sponsor all SAEs, regardless of whether the investigator believes they are related to the study drug.

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

7.2 Definitions

7.2.1 Definition of an Adverse Event

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

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

An AE includes medical conditions, signs, and symptoms not previously observed in the patient that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with an underlying condition that were not present prior to the AE reporting period (Section 7.3.1).

7.2.2 Definition of a Serious Adverse Event

A **serious adverse event** is any AE that results in any of the following outcomes:

- Death,
- A life-threatening AEs (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
- Other medically important events: based upon appropriate medical judgment, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not

result in inpatient hospitalization, or the development of drug dependency or drug abuse. These events must be reported to the Sponsor similar to serious adverse events.

- Safety events of interest ("Special Situations") on the medicinal products administered to the patient as part of the study (e.g., study drug, comparator, background therapy) that **may** require expedited reporting and/or safety evaluation include, but are not limited to:
    - Overdose of the medicinal product (exceeding the maximum allowable per dose, i.e., 400 mg or 3.5 mg/kg, whichever is lower)
    - Suspected abuse/misuse of the medicinal product
    - Inadvertent or accidental exposure to the medicinal product
    - Medication error involving the medicinal product (with or without patient/patient exposure to the Sponsor medicinal product, e.g., name confusion). However, non-clinically significant errors of this type would not require expedited reporting. The medical monitor should be contacted if any clarification is required.
    - Drug-drug interactions

7.3 Procedures for Eliciting, Recording, and Reporting Adverse Events

7.3.1 Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and ends 28 days after the last study visit, except for pregnancy reporting (Section 7.3.6).

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

Adverse events collected prior to dosing of study drug will be considered "nontreatment emergent" while those reported after the first dose of study drug and up to 28 days after the last dose of study drug will be considered "treatment emergent" and be assessed for relationship to study drug. If an AE starts on Day 1, the investigator must assess as to whether the AE started prior to or after the administration of study medication and record accordingly.

7.3.2 Adverse Event Eliciting/Reporting

During the AE reporting period, study site personnel will collect AEs in response to general questions about the patient's well-being and any possible changes from the baseline or previous visit, but shall not be specifically solicited. There will be no directed questioning for any specific AE. This does not preclude the site from collecting and recording any AEs reported by the patient to site personnel at any other time. Conditions including signs and symptom present at baseline, unless significantly worsened, should not be reported as adverse events during the study.

Whenever possible, diagnoses should be recorded when signs and symptoms are due to a common etiology, as determined by qualified medical study staff. New indications for medications started after informed consent is obtained until 28 days after the last dose of study

drug may qualify to be recorded as AEs; recurrence or worsening of medical history problems requiring new or changes in concomitant medication, may also qualify to be recorded as AEs.

An abnormality identified during a medical test (e.g., laboratory parameter, vital sign, ECG data, physical exam) should be defined as an AE only if the abnormality meets one of the following criteria:

- Induces clinical signs or symptoms
- Requires active intervention
- Requires interruption or discontinuation of study medication
- In the opinion of the investigator, the abnormality is clinically meaningful and significantly different from baseline.

The following attributes must be assigned to each AEs:

- 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 action (treatment, nondrug therapy) required
- Determination of "seriousness"

7.3.3 Assessing Adverse Event Severity

Adverse Events will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for AE (CTCAE) 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; clinical or diagnostic observations only; 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:** The patient died due to the event.

7.3.4 Assessing Relationship to Study Drug

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

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

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

- **Related (Adverse Reaction):**
  - Any event for which there is evidence to conclude that the study drug caused the event
- **Possibly Related (Suspected Adverse Reaction):**
  - A single occurrence of an event that is uncommon and *known to be strongly associated with exposure to a new drug,* such as angioedema, anaphylaxis, rhabdomyolysis, Stevens-Johnson syndrome, etc.
  - One or more occurrences of an event that is not commonly associated with drug exposure but is otherwise uncommon in the population exposed to the drug, such as tendon rupture
- **Not Related:**
  - The event represents the underlying disease (e.g., disease-related symptoms, disease progression)
  - The event represents a comorbid condition present at the time the patient entered the study
  - The event represents a known adverse reaction associated with a co-medication received by the study patient
  - The event is common for the study population (e.g., cardiovascular (CV) events in an elderly population)
  - The event has no plausible relationship to study drug
  - The event is a study endpoint (e.g., mortality, major morbidity)

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

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

7.3.5 Reporting Serious Adverse Events on the SAE Report Form

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

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

Full details of the SAE should also be recorded on the medical records and onto the eCRF. 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 (within seven days) as necessary.

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

7.3.5.1 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 Independent Ethics Committee (IEC) of SAEs in accordance with local regulations. Sponsor, or its safety representative, will provide to the investigator a copy of any expedited safety reports that it intends to file with a regulatory authority.

7.3.5.2 Deaths

For any death occurring during the patient's study participation, regardless of attribution, the investigator will report the death immediately to the Sponsor or its designee as a SAE.

The investigator should notify Sponsor or its designee of any death or other SAE occurring after a patient has discontinued or terminated study participation that may reasonably be related to the study.

The investigator must submit the SAE Report Form and complete the appropriate eCRF for the event that led to the patient's death.

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

7.3.6 Pregnancies: Reporting and Follow-up of Patients

A pregnancy in a female patient must be confirmed by a positive serum β-chorionic gonadotrophin test. If a female patient becomes pregnant while the patient is receiving study treatment or within 12 weeks after the last dose of study treatment, a Pregnancy Report Form must be completed and submitted to Sponsor or its designee within 24 hours of the investigator learning of the pregnancy. The investigator should report the information to the Sponsor on the designated forms. If applicable, a pregnant patient is immediately withdrawn from receiving study treatment. The investigator must follow the pregnancy to completion to ascertain both its outcome and whether any AEs occurred.

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. The outcome of the pregnancy must be reported by the investigator, which should be sent to the Sponsor and/or its designated safety management vendor within 24 hours of the investigator learning of the outcome. 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.

7.3.7 Abnormal Laboratory Findings

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

An abnormal laboratory finding should be defined as an AE only if the abnormality meets one of the following criteria:

- Induces clinical signs or symptoms
- Requires active intervention
- Requires interruption or discontinuation of study medication
- In the opinion of the investigator, the abnormality is clinically meaningful and significantly different from baseline

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.

A decrease in Hb value without any significant clinical symptoms should not be reported as an adverse event. In this case, worsening of anemia as evidenced by drop in Hb value may be considered as lack of efficacy as opposed to AE as the patient fails to respond adequately to study drug.

7.3.8 Disease Progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. Gradual worsening of MDS should be considered disease progression and should be reported as an AE during the study. Worsening of anemia, per se, should not be reported as disease progression because changes in Hb levels will be adequately monitored and assessed in the efficacy analyses.

8 STATISTICAL CONSIDERATIONS

Data from patients in the OL component of the study will be analyzed separately from the DB placebo randomized portion of the study.

Double-blind component

Descriptive statistics including number of patients (N), means, standard deviations, medians, and minimum and maximum values will be presented for continuous variables. Counts and percentages will be presented for categorical variables. For efficacy endpoints, the standard error and 95% confidence intervals will be presented as part of the descriptive summaries.

The Statistical Analysis Plan will provide in detail the analyses and summaries to be performed.

The rest of this section (8.1-8.4) pertains to the DB component.

8.1 Sample Size Determination

160 patients are planned to be randomized in a 3:2 ratio to roxadustat or matching placebo. This sample size will provide at least 90% power to demonstrate a statistically significant difference between roxadustat and placebo at the significance level of 0.05 using a two-sided Fisher's test, and assuming the response rates of the primary endpoint are 35% and 5% in roxadustat and placebo, respectively.

8.2 Randomization and Treatment Assignment

Patients will be randomized, stratifying by the following

- Serum EPO level: either ≤200 mIU/mL OR >200 mIU/mL and ≤400 mIU/mL
- IPSS-R low risk / very low risk vs. intermediate risk group classification
- RBC transfusion burden: 1 pRBC/8-weeks documented over 16 consecutive weeks vs 2-4 pRBC documented over 8 weeks. NOTE: 1-pRBC randomization will be limited to no more than 30% of the total randomized patient population

8.2.1 Full Analysis Set Population (FAS)

The FAS Population consists of all patients **randomized** to this study.

Analyses of efficacy data will be based on the FAS Population.

8.2.2 Safety Populations

The Safety Populations consist of all patients who have received at least one dose of study drug.

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

8.3 Statistical Analyses

8.3.1 Multiple Testing and Control of Family-Wise Type I Error

The statistical test results of the primary and secondary endpoints at the week 28 time point will be used to determine and describe the treatment efficacy of roxadustat. To control the family-wise type I error at the level of 0.05, a sequential gatekeeping procedure will be used to test the primary and secondary efficacy endpoints. Specifically, if the test of the primary endpoint is significant at the level of 0.05, the first secondary endpoint will be tested at the level of 0.05.

The order of testing of secondary endpoints will follow the order presented in Section 8.3.3.2. Other secondary endpoints will be tested conditioning on the previous endpoint achieving statistical significance, in the order listed in the Statistical Analysis Plan (SAP). Statistical testing will stop at the first endpoint that fails to achieve significance level. All statistical tests will be two-sided at the significance level of 0.05.

8.3.2 General Considerations

Descriptive summaries will be presented for study parameters including baseline characteristics, safety, and efficacy. Continuous variables will be reported in mean, standard deviation or standard error, median, minimum, and maximum.

Categorical variables will be reported by the frequency and percentage of patients within each outcome category.

Analyses of the efficacy data will be based on the FAS Population.

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

Safety data will be summarized descriptively based on the Safety Population.

8.3.3 Analysis of Efficacy Data

8.3.3.1 Analysis of the Primary Efficacy Endpoint

Treatment response rate defined as the proportion of patients who achieved transfusion-independence (TI) ≥56 consecutive days in the first 28-weeks of treatment will be summarized using the FAS Population and will be compared between the two treatment groups using the Cochran-Mantel-Haenszel (CMH) chi-square test, controlling for stratification factors.

If one or more of the levels of the stratification variables are underrepresented during enrollment resulting one or more of the (2×2×2) 8 strata having too few patients to meet the required per-strata sample size for the planned statistical methodology, then the stratification variable with the highest imbalance will not be included in the analysis. This practice will be followed for the primary, secondary and exploratory variables.

Two-sided 95% confidence interval (CI) of the odds ratio will also be presented.

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

8.3.3.2 Analysis of the Secondary Efficacy Endpoints

When all the randomized patients complete 28 weeks of treatment or have discontinued study medication before this time, the analysis of the primary efficacy endpoint and secondary endpoints will be performed. Only Sponsor personnel who are not directly involved with the study sites/patients will have access to the unblinded data. The blind will be maintained for study patients, PI, site staff and site monitoring personnel for the remainder of the study (to Week 52 plus a 4 week follow-up period).

All secondary and exploratory endpoints will be analyzed at both for the first 28 weeks of treatment and for the end of the 52-week study treatment period.

8.3.3.2.1 Proportion of Patients who Achieved ≥50% Reduction in Number of pRBC Transfusions over 8 Weeks Compared to Their Baseline for Any 8 Week Period During the Study (Factor of Erythroid Response)

The proportion of patients who achieved ≥50% reduction in number of pRBC transfusion over 8-weeks compared to their baseline for any 8 week period during the study will be summarized using the FAS Population and will be compared between the two treatment groups using the Cochran-Mantel-Haenszel (CMH) chi-square test, controlling for stratification factors.

Two-sided 95% confidence interval (CI) of the odds ratio will also be presented.

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

8.3.3.2.2 Cumulative Number of Patient-Exposure-weeks of TI over the first 28 Weeks of the Treatment Period

The Cumulative number of patient-exposure –week of TI over the first 28-weeks of the treatment period will be summarized and analyzed using the FAS Population. A non-parametric ANCOVA controlling for stratification factors will be used to compare between treatment groups.

8.3.3.2.3 Cumulative Number of pRBC Transfused over the first 28-weeks of the Treatment Period

The Cumulative number of pRBC transfused over the first 28-weeks of the treatment period will be summarized and analyzed using the FAS Population. A non-parametric ANCOVA controlling for stratification factors will be used to compare between treatment groups.

8.3.3.2.4 Proportion of Patients who Achieved TI for ≥20 consecutive Weeks (140 consecutive Days)

The proportion of patients who achieved TI for ≥20 Weeks (140 Days) will be summarized using the FAS Population and will be compared between the two treatment groups using the Cochran-Mantel-Haenszel (CMH) chi-square test, controlling for stratification factors.

Two-sided 95% confidence interval (CI) of the odds ratio will also be presented.

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

8.3.3.2.5 Mean Change from Baseline in EQ-5D-5L assessment

The mean change from Baseline in EQ-5D-5L assessment will be summarized and analyzed using the FAS Population. A mixed model repeated measures (MMRM) analysis of covariance model (ANCOVA) model, controlling for stratification factors and baseline value of the corresponding parameter, will be used to assess treatment difference.

8.3.3.2.6 Mean Change from Baseline in Functional Subscale of PROMIS

The mean change from Baseline in Functional Subscale of PROMIS will be summarized and analyzed using the FAS Population. A MMRM-ANCOVA model, controlling for stratification factors and baseline value of the corresponding parameter, will be used to assess treatment difference.

8.3.3.2.7 Mean Change from Baseline in Vitality Subscale of PROMIS

The mean change from Baseline in Vitality Subscale of PROMIS will be summarized and analyzed using the FAS Population. A MMRM-ANCOVA model, controlling for stratification factors and baseline value of the corresponding parameter, will be used to assess treatment difference

8.3.3.3 Analysis of Exploratory Efficacy Endpoints

The additional efficacy analyses will use the FAS Population.

Additional efficacy analyses of continuous endpoints will use an MMRM/ANCOVA model using baseline value and other stratification factors as covariates.

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

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

8.3.4 Patient Enrollment and Disposition

Patient enrollment and disposition will be presented for all enrolled. The total number and percent of patients who completed or discontinued, and reasons for early discontinuation, will be summarized by dose cohort or treatment group using the FAS Population.

8.3.5 Demographics and Baseline Characteristics

Demographic data and other patient characteristics as well as baseline disease characteristics will be summarized descriptively using the FAS and the Safety Populations.

8.3.6 Summary of Safety Data

Summary of safety data will be based on the Safety Population. Safety parameters include adverse events, N (%) patients progressing to AML, laboratory parameters, vital signs, ECG parameters, prior and concomitant medication use. For each safety parameter, the last assessment made prior to the first dose of study treatment will be used as the baseline, unless otherwise specified. In general, safety data will be summarized descriptively; no inferential statistical procedures will be applied.

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, and AEs of special interest 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.

8.3.7 Interim Analysis

No interim efficacy analysis is planned for the study prior to all patients completing 28 weeks of study treatment.

8.4 Statistical Analyses Plan

A detailed Statistical Analysis Plan (SAP) will be finalized prior to database lock of the primary efficacy analysis of the study after all patients have completed 28 weeks of treatment or terminated before this timepoint. Any significant changes to the analyses described in this protocol will be highlighted in the SAP and the Clinical Study Report.

9 DIRECT ACCESS TO SOURCE DOCUMENTS

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

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

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

10 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Data Quality Assurance

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

- Investigator meeting and/or investigator site initiation
- Routine study site monitoring
- Documented study and system training
- Electronic case report form (eCRF) and query review against source documents

10.2 Audit and Inspection

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

11 ETHICS

11.1 Ethical Considerations

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

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

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

Investigators must also enter the names of the staff that are involved in the study on the Delegation of the Authority form and sign the form (including their responsibilities). This form must be updated when responsibilities of the staff change.

11.3 Informed Consent Form

No study procedure may be implemented prior to obtaining a signed, written Informed Consent Form (ICF) from the patient or the patient's legally authorized representative. IRB review and approval are required for the ICFs. The final IRB/IEC approved ICFs must be provided to FibroGen for regulatory purposes.

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

11.4 Patient Confidentiality

Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health information, 45 Code of Federal Regulations (CFR) Parts 160 and 164, and HIPAA.

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.

12 DATA HANDLING AND RECORD KEEPING

12.1 Source Documents

Source documents are original documents, data, and records that are relevant to the clinical study. The investigator will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each patient enrolled in this clinical study. Source documents must be adequate to reconstruct all data entered into the electronic database and used to resolve queries.

12.2 Data Collection, Handling, and Verification

All required data will be entered into an electronic database by authorized site personnel. Data will be entered into a validated, clinical database compliant with 21 CFR Part 11 regulations. The database will be a secured, password-protected system with full audit trail.

All 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 WHODrug).

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

13 FINANCING AND INSURANCE

Financing and insurance are addressed in a separate document.

14 PUBLICATION POLICY

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

15 INVESTIGATOR REQUIREMENTS

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

15.1 Study Drug Accountability

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

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

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

15.2 Disclosure of Data

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

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

15.3 Retention of Records

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

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

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17 APPENDICES

Appendix A – Schedule of Assessments: Screen to Week 52, Including EOT Assessments for Patients Completing 52 weeks Treatment

Procedures	Screening		Treatment Weeks																							Post-EOT[19]
	28 days		±1 day					±2 days																		
	S1	S2	Week 1 Day 1	2	3	4	5	7	9	11	13	15	17	19	21	23	25	27	28	31	35	39	43	47	52 EOT[17]	WK4
Informed consent signature	X																									
Eligibility Review[1]	X		X																							
Med History/ Demographics	X																									
Physical Exam	X																		X						X	X
Weight[6]	X		X																X							
HbsAg, anti-HCV AB, HIV	X																									
Endogenous serum EPO Level[2]	X		X				X								X		X		X			X			X	X
B12, Folate	X																		X						X	X
PK[3]			X				X								X		X									
ECG[4]	X																		X						X	X
Bone marrow aspirate and biopsy[5]	X																								X	
Vital signs[6]	X		X				X		X		X		X		X		X		X			X			X	X
ECOG Score[7]	X	X	X				X				X		X				X		X						X	X
Serum Lipid Panel			X				X								X				X			X			X	X
LFTs [8]	X	X	X		X		X		X		X		X		X		X		X			X			X	X
Serum chemistry[9]	X		X				X		X		X		X		X		X		X			X			X	X
PT, PTT	X		X																X						X	X
Hepcidin	X		X				X				X				X		X		X			X			X	X
Pregnancy test[10]	X		X																						X	X
Point-of-care Urine Pregnancy Test[10]											X						X					X				
C-reactive protein			X																X						X	X
Recording of transfusions[11]	→																									
CBC[12]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Local Hemoglobin			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Reticulocyte count; CHr	X						X		X		X		X		X		X		X			X			X	X
Iron Biomarkers[13]	X		X				X		X		X		X		X		X		X			X			X	X
Registration/Randomization[14]			X																							
HRQoL Questionnaires[15]			X						X				X						X						X	X
Study drug dosing[16]			DOSE THREE TIMES PERWEEK →																							
Study drug dispensation[17]			X		X		X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X		
Dose adjustment review[18]									X		X		X		X		X			X	X		X			
AEs/Con Meds/Procedures	→																									

1. Eligibility review: pre-transfusion Hb measurements will be obtained via review of source document, must be obtained within 72-hours prior to transfusion; baseline Hb level will be obtained 3 to 10 days prior to registration/randomization; GFR will be done prior to registration/randomization (see Appendix L)
2. Serum erythropoietin level must be ≤400 mIU/mL at screening; during the last month of treatment a serum EPO level will be drawn just prior to the next study drug dosing; patients should be told to not take their study drug until after the study visit on that day.
3. PK: see Appendix J. Levels at 1-3 and 3-5 hours after dosing at clinic on Day 1 (Week 1) as well as 4-6 hours at Week 5 and 8-10 hours at Week 21 after administration at the clinic. Two samples will be obtained 0-2 hours before dosing and 2-3 hours after dosing at Week 25; vital signs will also be taken prior to the time of the PK draw
4. ECG: no clinically significant findings per PI review at screen period
5. Patients will need to have the results from the bone marrow exam and cytogenetic analysis performed for the IPSS-R criteria. Report and slides must be available for centralized review. Bone marrow exam will be done within 4 weeks of end of treatment on all patients
6. Vital signs include BP, HR, RR, temperature. These will also be done prior to each PK sample taken. If possible, use the same device for BP measurement over the course of the study. Weight at registration/randomization will be used for determination of starting dose.
7. ECOG score: must be 0,1, or 2 at last screen visit
8. LFTs = AST, ALT, TBili, alkaline phosphatase. ALT >3 x ULN, OR AST >3 × (ULN), OR TBili > 1.5 × ULN will exclude a subject from entering the study (see Appendix H and Appendix O for liver monitoring information)
9. Serum chemistry = sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, magnesium, phosphorus, LDH, albumin (Central Lab) – see Appendix K
10. Pregnancy Test: must be negative for women of child bearing capacity at screening. Additional pregnancy testing for women of child bearing capacity will also be done at Weeks 13, 25, 39, EOT and Post-EOT visits.
11. Recording of Transfusions: all RBC transfusions from 8 to16 weeks prior to first dose throughout end of treatment. For study entry, patients are considered to have LTB if they received 1 to 4 pRBC within 8 weeks prior to registration/randomization. Patients with 1 pRBC/8weeks must have a documented history of requiring 1 pRBC/8weeks in at least 2 consecutive 8 weeks periods in the 16 weeks preceding registration/randomization. Pre and post transfusion Hb will be collected at 8 weeks post-registration/randomization. The PI and site staff will utilize their own institutional criteria for the determination of when to transfuse a patient. **Open-Label patients only**, the requirement to demonstrate transfusion dependence can also be met by a PI starting this particular patient on pRBC transfusion during the screening period.
12. 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.
13. Iron biomarkers = serum iron, ferritin, TIBC, TSAT, and UIBC.
14. Registration into the OL component or Randomization into the DB component to occur on Day 1, Week 1 prior to first dose which should be given at the site
15. HRQoL questionnaires include PROMIS and EQ-5D-5L. ONLY for patients randomized to DB study
16. 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/placebo (study medication) can be taken with water with or without food. The dose of statins should not exceed the protocol-recommended daily dose in the protocol.
17. Last dose of study drug must be prior to EOT assessments
18. Dose adjustment review every 8 weeks for upward adjustments. Week 9 evaluation requires determination of Erythroid Response. A re-assessment will be done for these patients at Week 12 and if TI is observed the dose will not be increased.
19. Must be at least 28 days post-dose/EOT

Appendix B – Patients who Discontinue Study Medication Prior to Week 52

Procedures	EOT[17]	Post - EOT[19]	Every 8 weeks assessment from Post-EOT WK 4 visit. Last visit at Week 52 from first dose.	
		WK 4	WK 12	→
Informed consent signature				
Eligibility Review[1]				
Med History/ Demographics				
Physical Exam	X	X		
Weight[6]				
HbsAg, anti-HCV AB, HIV				
Endogenous serum EPO Level[2]	X	X	X	
B12, Folate	X	X		
PK[3]				
ECG[4]	X	X		
Bone marrow aspirate and biopsy[5]	X			
Vital signs[6]	X	X	X	
ECOG Score[7]	X	X		
Serum Lipid Panel	X	X		
LFTs[8]	X	X	X	
Serum chemistry[9]	X	X	X	
PT, PTT	X	X		
Hepcidin	X	X	X	
Pregnancy test[10]	X	X		
C-reactive protein	X	X		
Recording of transfusions[11]	→			
CBC[12]	X	X	X	
Local Hemoglobin	X	X	X	
Reticulocyte count; CHr	X	X		
Iron Biomarkers[13]	X	X	X	
Registration/Randomization to the study				
HRQoL Questionnaires[15]	X	X		
Study drug dosing				
Study drug dispensation				
Dose adjustment review				
AEs/Con Meds/Procedures	→			

For footnotes please refer to Appendix A

Appendix C – Dose Adjustment Rules During the Titration to Achieve TI – Correction Phase (Prior to Maintenance Phase)

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.

In the OL component, cohort 1 (n=8) starts at 1.5 mg/kg, (Dose Level 1) followed by cohort 2 (n=8) at 2.0 mg/kg (Dose Level 2) and finally cohort 3 (n=8) at 2.5 mg/kg (Dose Level 3). The optimal starting dose will be selected for the DB component following evaluation of the OL data. It is anticipated that for the DB component, the starting dose level will be level 2 (2.0 mg/kg) and the protocol is written to reflect this but if the OL data identifies level 1 or 3 as a more optimal starting dose, this will be implemented.

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 next 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.

** Patients with body weight ≥ 120 kg will receive fixed dose of 400 mg TIW at Dose Level 3.

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

Dose Escalation

Following commencement of study treatment, patients are evaluated for response after 8 weeks and, if the patient has required one or more RBC transfusion in that period then the dose is increased by one dose level. After each dose adjustment, the patient remains on the dose level for a minimum of 8 weeks before further adjustment is permitted.

With the exception that the starting dose will be maintained if an erythroid response (defined as a 50% reduction in pRBC from baseline) is seen after the initial 8 weeks of dosing. A re-assessment will be done for these patients at week 12 and if transfusion independence (TI) is observed the dose will not be increased. If TI is NOT observed at this point, the dose will be increased by one dose level.

Dose Reduction

The down titration of the study treatment is allowed at any time but must be performed if any of the following criteria are met. Hb levels should be retested for confirmation every 2 weeks after a dose reduction, however it is per investigator's discretion:

a) Transfusion independent for ≥56 days consecutively and Hb ≥12 g/dL; or

b) Transfusion independent for ≥56 days consecutively and the rate of rise of Hb ≥2.5 g/dL over 4 weeks.

c) In the instance where the patient achieved TI in the initial 8-weeks of the study, or has undergone treatment with the maximum allowable dose, i.e., 400 mg TIW or 3.5 mg/kg for at least 8-weeks, patient may undergo dose reduction by 1-dose level. If there were no difference in erythroid response (same transfusion burden and Hb was unchanged) at this dose level for 8-weeks compared to another lower dose level, investigator may contact Sponsor's Medical Monitor to discuss another potential dose reduction.

This is an effort to treat patients with the lowest effective dose needed to maintain erythroid response; thus, study drug dose can be increased again if erythroid response appeared to be decreased with dose decrease.

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

Appendix D – Dose Adjustment Rules for Patients who have TI for ≥56 Days (8 weeks) – Maintenance Phase

A modified dose adjustment algorithm will apply to patients who have attained TI ≥56 days. The down titration of the dose is allowed at any time.

<table>
<tr><th></th><th colspan="4">Hemoglobin (Hb) Values</th></tr>
<tr><th>Change in Hb from 4 weeks earlier (g/dL)</th><th>Hb <10.5 g/dL</th><th>Hb 10.5 to 12.9 g/dL</th><th>Hb >13.0 g/dL</th><th>Hb ≥13.5 g/dL</th></tr>
<tr><td>< -1.0 * (or had RBC transfusion within 4 weeks)</td><td>↑</td><td>↑</td><td>No change</td><td rowspan="3">Hold, then resume dosing when:
Hb <12 g/dL, at a dose that is reduced by one-dose level

Patients are to return weekly to monitor Hb until dosing can be resumed</td></tr>
<tr><td>-1.0 to 1.0</td><td>↑</td><td>No change</td><td>↓</td></tr>
<tr><td>> 1.0</td><td>No change**</td><td>↓</td><td>↓</td></tr>
</table>

* 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

****Dose Adjustment for Excessive Hematopoiesis During Maintenance Phase:**
At any time during the Treatment Period of the maintenance phase if Hb increases by >2.0 g/dL within 4 weeks, the dose should be reduced by one dose level.

Appendix E – Quality of Life Assessments

The following health-related quality of life (HRQoL) assessment tools will be utilized for this study:

1. Patient-Reported Outcomes Measurement Information System (PROMIS®, Cella et al. 2007; Cella et al., 2010)
2. European Quality of Life Five Dimensional Health Questionnaire (EQ-5D-5L), (Rabin and de Charro, 2001)

The rationale for each of the PRO items and domains selected includes consideration of the applicable concepts to be evaluated and context of use for this study.

Specific symptoms that are most important to the MDS population are fatigue/tiredness. Currently, there are no existing perfect measures to capture these symptoms.

PROMIS provides clinicians and researchers access to reliable, valid, and flexible measures of health status that assess physical, mental, and social well–being from the patient perspective. PROMIS measures are standardized, allowing for assessment of many patient-reported outcome domains, including pain, fatigue, emotional distress, physical functioning and social role participation, based on common metrics that allow for comparisons across domains, across chronic diseases, and with the general population. Further, PROMIS tools allow for computer adaptive testing, efficiently achieving precise measurement of health status domains with few items. There are PROMIS measures for both adults and children. PROMIS was established in 2004 with funding from the National Institutes of Health (NIH) as one of the initiatives of the NIH Roadmap for Medical Research.

EQ-5D is a standardized instrument for measuring generic health status. The health status measured with EQ-5D is used for estimating preference weight for that health status, then by combining the weight with time, quality-adjusted life year (QALY) can be computed. QALYs gained is used as an outcome in cost-utility analysis which is a type of economic evaluation that compares the benefit and cost of health care programs or interventions. Many countries generated a value set (preference weights) of their own population and have used it for estimating QALY to make decisions in resource allocation. There are currently 171 language versions of EQ-5D questionnaire available. EQ-5D is one of the most commonly used generic health status measurement, and its good validity and reliability have been reported in various health conditions.

Importantly, PROMIS is a validated instrument for the MDS population (Abel et al., 2014), and so is EQ-5 (Efficace, 2015).

References:

Abel et al. (2014) Patient-reported outcomes for the myelodysplastic syndromes: a new MDS-specific measure of quality of life. Blood 123:451-452

Cella D, Yount S, Rothrock N, et al. (2007) The Patient-Reported Outcomes Measurement Information System (PROMIS): Progress of an NIH Roadmap Cooperative Group During its First Two Years. Medical Care. **45**:(5):S3-S11

Cella D, Riley W, Stone A, et al. on behalf of the PROMIS Cooperative Group (2010) Initial adult health item banks and first wave testing of the patient-reported outcomes measurement information system (PROMIS™) Network: 2005–2008. J Clin Epidemiol 63 (11):1179-1194

Efficace et al (2015) Prevalence, severity and correlates of fatigue in newly diagnosed patients with myelodysplastic syndromes. Br J Haematol 168:361-370

Rabin and de Charro (2001) EQ-5D: a measure of health status from the EuroQol Group. Ann Med 33:337-343

Appendix F – 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 G – International Prognostic Scoring System – Revised (IPSS-R)

International Prognostic Scoring System

Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very Good		Good		Intermediate	Poor	Very Poor
BM* Blast %	≤2		>2-<5%		5-10%	>10%	
Hemoglobin	≥10		8-<10	<8			
Platelets	≥100	50-<100	<50				
ANC**	≥0.8	<0.8					

* bone marrow
** absolute neutrophil (white blood cell) count

IPSS-R Risk Groups

Risk Group	Risk Score
Very Low	≤1.5
Low	> 1.5-3
Intermediate	> 3-4.5
High	> 4.5-6
Very High	> 6

Appendix H – 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 I – 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 J – Schedule of PK Assessments

Timing and Number of PK Samples; note that Vital Signs will be taken prior to each blood draw

	0-2 hrs pre-dose^	1-3 hrs	2-3 hrs	3-5 hrs	4-6 hrs	8-10 hrs
Day 1 (Week 1)		1		1		
Week 5					1	
Week 21						1
Week 25	1		1			

^Time points are post-dose unless specified otherwise

Appendix K – Laboratory Tests

CBC:	**Serum Chemistry:**
Basophils	Albumin
Eosinophils	Bicarbonate
Erythrocyte count (RBC)	BUN
HCT	Calcium
Hb	Chloride
Leukocyte count (WBC)	Creatinine
Lymphocytes	Glucose
Mean corpuscular volume	Lactate dehydrogenase
Mean corpuscular Hb	Magnesium
Mean corpuscular Hb concentration	Phosphorus
Monocytes	Potassium
Neutrophils	Na
Neutrophils, immature (banded)	
Platelets	
Iron Biomarkers:	**LFTs:**
Ferritin	ALP
Iron	ALT
TIBC	AST
UIBC	TBili
TSAT	
Additional Hematology Analytes:	**HIV and Viral Hepatitis Panel:**
Reticulocyte count	Anti-HCV Ab tests
CHr	HBsAg
	HIV
Special Laboratory Tests:	
Hepcidin	CRP
Serum erythropoietin level	PT
Serum Lipid Panel (non-fasting) including total cholesterol, LDL and TG	PTT
	Vitamin B_{12} and folate
Point-of-care Urine Pregnancy Test	Serum Pregnancy

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; CHr = reticulocyte hemoglobin content; Hb = hemoglobin; HBsAg = hepatitis B surface antigen; HCT = hematocrit; HCV = hepatitis C virus; HIV = human immunodeficiency virus; LDH = lactate dehydrogenase; LDL = low density lipoprotein; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell; TBili = total bilirubin; TG = triglycerides; TIBC = total iron binding capacity; UIBC=unsaturated iron binding capacity TSAT = transferrin saturation; WBC = white blood cell.

Appendix L – Calculation of Creatinine Clearance/eGFR per Cockroft-Gault

The Cockcroft-Gault (CG) formula (Cockroft and Gault, 1976; Gault, 1992) estimates GFR in ml/min and employs serum creatinine measurements and a patient's weight to predict the creatinine clearance as follows:

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times [0.85 \; if \; Female]}{72 \times \text{Serum Creatinine (in mg/dL)}}$$

When serum creatinine is measured in µmol/L, the following formula applies:

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times Constant}{\text{Serum Creatinine (in } \mu\text{mol/L)}}$$

Where Constant is 1.23 for men and 1.04 for women.

A web-based Cockroft-Gault calculator can be accessed at http://nephron.com/cgi-bin/CGSI.cgi.

References:

Cockcroft DW, and Gault MH (1976). Prediction of creatinine clearance from serum creatinine. Nephron **16**: (1): 31–41

Gault MH, Longerich LL, Harnett JD, and Wesolowski C (1992). Predicting glomerular function from adjusted serum creatinine. Nephron **62**: (3): 249–256

Appendix M – New York Heart Association Classification (NYHA) of Congestive Heart Failure

The list below describes the most commonly used classification system, the NYHA Functional Classification. It places patients in one of four categories based on how much they are limited during physical activity.

Class	Patient Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g., no shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g., walking short distances (20–100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

Reference:

The Criteria Committee of the New York Heart Association (1994). Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels (9th ed.). Boston: Little, Brown & Co. pp. 253–256.

Appendix N – Blood Pressure and Heart Rate Monitoring

Blood Pressure

Blood pressure (BP) measurement should be done with the patient comfortably seated in a chair, with the legs uncrossed, and the back and arm supported, such that the middle of the cuff on the upper arm is at the level of the right atrium (the midpoint of the sternum). The patient should be instructed to relax as much as possible and to not talk during the measurement procedure. Preferably measurement will be done with an electronic automated device. The same device should preferably be used for the patient during the course of the study, timing as indicated in the Schedule of Assessments. Also the same arm should be used consistently for readings throughout the study.

Heart Rate

Heart rate measurement should be done at rest in a sitting position wherever possible. It can be performed with an electronic automated device as used for BP measurement. The same device should preferably be used for the patient during the course of the study, timing as indicated in the schedule of assessments.

Appendix O – Individual Patient Study Stopping Criteria

Patients will be discontinued from treatment for the following reasons:

a. Disease progression: Diagnosis of AML during the study
b. Liver Function: Discontinuation of treatment will occur 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%)