Phase 2 Study of Oral Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitor Roxadustat for the Treatment of Anemia in Patients with Chronic Kidney Disease - 16 to 24 Weeks

SUPPLEMENTARY MATERIAL

Supplemental Table 1: Inclusion and Exclusion Criteria

Inclusion Criteria	1. Age 18 to 75 years; subjects older than 75 years of age may be permitted on a case-by-case basis, at the discretion of the FibroGen medical monitor 2. Chronic kidney disease, not receiving dialysis, with an estimated glomerular filtration rate (eGFR) of ≥15 and <60 mL/min/1.73 m^2 (KDOQI Stage 3 or 4), estimated using the abbreviated 4-variable MDRD (Modification of Diet in Renal Disease) equation. Subjects with eGFR <15 mL/min/1.73 m^2 (KDOQI Stage 5) may be permitted on a case-by-case basis, at the discretion of the FibroGen medical monitor 3. Ferritin >30 ng/mL 4. TSAT ≥5% 5. Mean of the two most recent hemoglobin values during the screening period, obtained at least 7 days apart, must be ≤10.5 g/dL, with a difference of ≤1.0 g/dL between the two values 6. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) must be ≤2x upper limit of normal (ULN) at screening 7. Total bilirubin (Tbili) must be ≤ULN at screening 8. Alkaline phosphatase (ALP) must be <2x ULN 9. Screening serum folate and vitamin B_{12} level ≥lower limit of normal 10. Body weight 45 to 140 kg
Exclusion Criteria:	1. Received any ESA or more than one dose of IV iron within 12 weeks prior to randomization 2. Any clinically significant infection or evidence of an underlying infection, as manifested by a total white blood cell (WBC) count >ULN, within 4 weeks prior to randomization 3. Positive for any of the following: human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or antihepatitis C virus antibody (anti-HCV Ab) 4. History of chronic liver disease 5. Serum albumin <3 g/dL 6. New York Heart Association Class III or IV congestive heart failure

Exclusion Criteria (cont.)	7. Myocardial infarction or acute coronary syndrome within 12 weeks prior to randomization 8. Thromboembolic event within 12 weeks prior to randomization 9. Uncontrolled hypertension (systolic BP >170 mm Hg or diastolic BP >110 mmHg) within 4 weeks prior to randomization 10. Diagnosis or suspicion (e.g., complex kidney cyst of Bosniak Category II or higher) of renal cell carcinoma on renal ultrasound within 3 months prior to randomization 11. History of malignancy, except the following: cancers determined to be cured or in remission for ≥5 years, curatively resected basal cell or squamous cell skin cancers, cervical cancer in situ, or resected colonic polyps 12. Chronic inflammatory disease that could impact erythropoiesis (e.g., systemic lupus erythematosis, rheumatoid arthritis, celiac disease) even if it is currently in remission 13. Active or chronic gastrointestinal bleeding, or a known coagulation disorder 14. Hemoglobinopathy (e.g., homozygous sickle-cell disease, thalassemia of all types, etc.) 15. History of myelodysplastic syndrome, multiple myeloma, or pure red cell aplasia 16. History of hemosiderosis, hemochromatosis or polycystic kidney disease 17. Active hemolysis or diagnosis of hemolytic syndrome 18. Known bone marrow fibrosis 19. Uncontrolled or symptomatic secondary hyperparathyroidism 20. Seizure disorder or receiving anti-epilepsy medication for seizure disorder within 12 weeks prior to randomization 21. Known proliferative retinopathy 22. Any prior or scheduled organ transplantation 23. Anticipated elective surgery that is expected to lead to significant blood loss during the study period 24. Life expectancy <12 months 25. Drug-treated gastroparesis, short-bowel syndrome, or any other gastrointestinal condition that may lead to reduced absorption of study drug 26. Anticipated use of dapsone or acetaminophen >2.0 g/day, or >500 mg per dose repeated every 6 hours, during the Treatment or Follow-Up Periods of the study 27. Androgen, deferoxamine, deferiprone, or deferasirox therapy within 12 weeks prior to randomization 28. Red blood cell transfusion within 8 weeks prior to randomization or anticipated need for transfusion during the treatment period

Exclusion Criteria (cont.)	29. History of alcohol or drug abuse within a year prior to randomization, or anticipated inability to avoid consumption of more than three alcoholic beverages per day 30. Prior treatment with FG-4592 or any hypoxia-inducible factor prolyl hydroxylase inhibitor 31. Use of an investigational medication or treatment, participation in an investigational interventional study, or carryover effect of an investigational treatment expected, within 4 weeks prior to randomization 32. Pregnant or breastfeeding females 33. Females of childbearing potential, unless using contraception as detailed in the protocol; male subjects with sexual partners of childbearing potential who are not on birth control unless the male subject agrees to use contraception 34. Any medical condition that in the opinion of the investigator may pose a safety risk to a subject in this study or which may interfere with study participation

Supplemental Table 2: Dose and Dose Frequency Adjustment Rules

Dose adjustment rules were built into the study protocol to enable investigators to adjust the dose for their subjects to achieve correction of anemia and maintain their Hb levels within a predefined target range. The dose adjustment rules were as follows:
• No dose adjustment occurred during first 4 study weeks, except in the event of excessive hematopoiesis (when the subject's dose should be reduced) and dose frequency conversion (see below).
• Dose adjustment reviews could occur from Week 5 onward, and every 4 weeks thereafter. In contrast, dose frequency conversions could occur at any dosing week (even during first 4 study weeks, if indicated).
• The time interval between dose adjustment reviews was 4 weeks in Cohorts A through F, except in the event of excessive hematopoiesis. Even if a subject's dose was not increased or decreased following a dose adjustment review at end of study week 8, the next dose adjustment review occurred 4 weeks after the last dose adjustment review, i.e., after 12 weeks.
• Subjects in Cohorts B and F whose two consecutive Hb levels reached 11.0 g/dL AND increased at least 1.0 g/dL from baseline were converted from TIW to BIW dosing at the start of a new week of dosing. Thus, a subject who required a roxadustat dose of 60 mg TIW was converted to a dose of 60 mg BIW. During this conversion, and for 4 weeks after conversion, no further dose adjustment occurred.
• Subjects in Cohort E whose two consecutive Hb levels reached 11.0 g/dL and were at least 1.0 g/dL above baseline were converted from BIW to QW with a dose step increase at the start of a new week of dosing. For 4 weeks after conversion, no further dose adjustment occurred.
• Additionally, subjects in Cohort F on BIW maintenance dosing who maintained constant study drug doses with stable Hb values between 11.0 and 13.0 g/dL for at least 8 weeks had their dose frequency reduced further to QW with a dose step increase at the start of a new week of dosing, provided the maximum study drug dose of 2.5 mg/kg was not exceeded. For 4 weeks after conversion, no further dose adjustment occurred.
• Dose adjustment rules in Cohorts A, B, E, and F were based on changes in Hb values over 4 weeks, and whether the Hb target has been reached or exceeded.
• Dose adjustment rules in Cohorts C and D were based on changes in Hb values over 4 weeks, and whether the Hb was below 10.5 g/dL or had reached or exceeded 12.0 g/dL.
• The maximum study drug dose was capped at 2.2 mg/kg for Cohorts A through D, and at 2.5 mg/kg for Cohorts E and F onwards.
Dose Adjustments for Excessive Hematopoiesis:
• First 21 days of Treatment Period: if, at Day 22 or earlier, Hb has increased >1.5 g/dL from the baseline Hb value, reduce dose by approximately 50% of the initial dose
• At any time during the Treatment Period: if Hb increases by >2.0 g/dL in 2 weeks, dose should be reduced by approximately 50%. If more than one dose reduction rule applies, the rule that requires the largest dose reduction supersedes all other dose adjustment rules.
• If Hb >14 g/dL, dose was held and resumed at two dose steps below after Hb had declined below 12 g/dL.

Supplemental Table 3: Schedule of Assessments and Extent of Missing Data

Day	Scr	Scr	1	8	15	22	29	36	43	50	57	64	71	78	85	92	99	106	113	120	127	134	141	148	155	162	169	2 weeks	4 weeks	N	% missing data*			
Weeks	1	2	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	post-EOT	post-EOT		mean (SD)	median	IQR	range
Hb	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	x	x	x	143	6.3 (14.7)	0	0 - 6	0 - 88
Serum Iron	x		x								x								x								x		x	143	11.4 (16.7)	0	0 - 25	0 - 75
TSAT	x		x								x								x								x		x	143	11.5 (16.8)	0	0 - 25	0 - 75
Ferritin	x		x								x								x								x		x	143	12.1 (17.3)	0	0 - 25	0 - 75
TIBC	x		x								x								x								x		x	143	11.7 (16.8)	0	0 - 25	0 - 75
sTfR			x								x								x								x		x	138	11.7 (17.3)	0	0 - 25	0 - 75
CHr			x								x								x								x		x	136	13.5 (18.8)	0	0 - 25	0 - 75
MCV	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	x	x	x	143	6.3 (14.7)	0	0 - 6	0 - 88
Platelets	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	x	x	x	143	7.1 (14.8)	0	0 - 8	0 - 88
TC			x								x								x								x		x	143	11.2 (16.7)	0	0 - 25	0 - 75
HDL-C			x								x								x								x		x	30	37.8 (15.6)	50	25 - 50	0 - 50
LDL-C			x								x								x								x		x	30	38.6 (15.6)	50	25 - 50	0 - 50
Hepcidin			x								x								x								x		x	137	12.7 (20.1)	0	0 - 25	0 - 75
CRP			x								x								x								x		x	137	11.9 (18.0)	0	0 - 25	0 - 75

The 17-24 week time points were for Cohorts C-F, as Cohorts A & B were treated with roxadustat for 16 weeks only. Abbreviations: Scr 1, first screening visit; Scr 2, second screening visit; EOT, end of treatment; Hb, hemoglobin; TSAT, transferrin saturation, TIBC, total iron binding capacity; sTfR, soluble transferrin receptor; CHr, reticulocyte Hb content; MCV, microcorpuscular volume; TC, total cholesterol; HDL-C, high density lipoprotein-associated cholesterol; LDL-C, low density lipoprotein-associated cholesterol; CRP, c-reactive protein. N refers to total number of evaluable patients. *The % of missing data is first assessed on a per-patient basis by lab parameter for the treatment period (Weeks 0-16 for Cohorts A & B and Weeks 0-24 for Cohorts C-F) using the formula: % missing = (# of observations available for analysis) ÷ (# of observations expected). Then the data are summarized across all patients by parameter. For example, under % missing data for Hb, the mean represents the percent of observations missed averaged over all N patients with a range of 0-88% but an IQR of only 0-6%. Since efficacy evaluable subjects could be established as quickly as after 2 weeks of treatment, subjects who dropped out early for whatever reason would have the largest percent of missing values.

Supplemental Table 4: Change from Baseline in Iron Utilization Parameters in Efficacy-Evaluable Population Overall

Mean (SD) Levels	Baseline (n=143)	Change from Baseline			
		16 Weeks (n=103)	P-Value	EOS (n=122)	P-Value
Hepcidin (ng/mL)[1]	119.7 (107.6)	-27.7 (107.2)	0.004	21.7 (94.9)	0.017
Serum iron (µg/dL)	64.0 (21.7)	1.1 (30.0)	n. s.	14.3 (25.6)	<0.001
TSAT (%)	22.0 (7.7)	−2.7 (8.6)	0.002	4.3 (8.3)	<0.001
Ferritin (ng/mL)[2]	278 (246)	−85.9 (112.6)	<0.001	−45 (113)	<0.001
TIBC (µg/dL)[3]	261.5 (50.7)	40.4 (41.0)	<0.001	5.3 (35.7)	n. s.
MCV (fL)[4]	93.4 (6.1)	1.2 (4.5)	0.001	0.1 (4.6)	n. s.
CHr (pg)[5]	30.7 (2.4)	0.2 (2.0)	n. s.	1.3 (1.7)	<0.001
Platelets ($x10^9$/L)[6]	255 (88)	−12.5 (61.2)	0.008	-26.0 (52.3)	<0.001

All cohorts were combined. Baseline is defined as the mean of the last three available values pre-1st dose. P-values are from ANOVA model comparing change from BL with zero utilizing the pooled variance from all groups. EOS (end of study) was 4 weeks post-end of treatment. [1]n=137, 102, and 116, respectively. [2]n=143, 103, and 123, respectively. [3]TIBC: total iron binding capacity, n=145, 102, and 122 (Safety Population), respectively. [4]n=143, 128, and 127, respectively. [5]n=136, 96, and 117, respectively. [6]n=143, 128 and 128, respectively.

Supplemental Table 5: Number (%) of Subjects with Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term

System Organ Class* / Preferred Term^	Cohort A (N=24) n (%)	Cohort B (N=24) n (%)	Cohort C (N=24) n (%)	Cohort D (N=24) n (%)	Cohort E (N=24) n (%)	Cohort F (N=25) n (%)	Total (N=145) n (%)
Number of Subjects with SAEs	**3 (12.5)**	**4 (16.7)**	**4 (16.7)**	**4 (16.7)**	**10 (41.7)**	**10 (40.0)**	**35 (24.1)**
Cardiac Disorders	**1 (4.2)**	**0**	**2 (8.3)**	**1 (4.2)**	**1 (4.2)**	**5 (20.0)**	**10 (6.9)**
Cardiac Failure Congestive	0	0	1 (4.2)	1 (4.2)	0	3 (12.0)	5 (3.4)
Cardio-Respiratory Arrest	0	0	1 (4.2)	0	1 (4.2)	0	2 (1.4)
Acute Myocardial Infarction	1 (4.2)	0	0	0	0	0	1 (0.7)
Atrial Fibrillation	0	0	0	0	0	1 (4.0)	1 (0.7)
Myocardial Infarction	0	0	0	0	0	1 (4.0)	1 (0.7)
Renal and Urinary Disorders	**0**	**1 (4.2)**	**1 (4.2)**	**1 (4.2)**	**2 (8.3)**	**2 (8.0)**	**7 (4.8)**
Renal Failure Acute	0	1 (4.2)	1 (4.2)	0	1 (4.2)	1 (4.0)	4 (2.8)
Renal Failure Chronic	0	0	0	1 (4.2)	0	1 (4.0)	2 (1.4)
Renal Impairment	0	0	0	0	1 (4.2)	0	1 (0.7)
Gastrointestinal Disorders	**1 (4.2)**	**0**	**1 (4.2)**	**1 (4.2)**	**2 (8.3)**	**1 (4.0)**	**6 (4.1)**
Pancreatitis	1 (4.2)	0	0	1 (4.2)	1 (4.2)	0	3 (2.1)
Abdominal Pain Lower	0	0	1 (4.2)	0	0	0	1 (0.7)
Diabetic Gastroparesis	0	0	1 (4.2)	0	0	0	1 (0.7)
Haematemesis	0	0	0	0	1 (4.2)	0	1 (0.7)
Pancreatitis Acute	0	0	0	0	0	1 (4.0)	1 (0.7)
Infections and Infestations	**1 (4.2)**	**1 (4.2)**	**0**	**0**	**1 (4.2)**	**3 (12.0)**	**6 (4.1)**
Cellulitis	0	0	0	0	1 (4.2)	2 (8.0)	3 (2.1)
Abscess	0	0	0	0	0	1 (4.0)	1 (0.7)
Bronchopneumonia	1 (4.2)	0	0	0	0	0	1 (0.7)
Pneumonia	0	1 (4.2)	0	0	0	0	1 (0.7)
Metabolism and Nutrition Disorders	**0**	**0**	**1 (4.2)**	**1 (4.2)**	**1 (4.2)**	**3 (12.0)**	**6 (4.1)**
Hyponatraemia	0	0	1 (4.2)	1 (4.2)	0	1 (4.0)	3 (2.1)
Diabetic Ketoacidosis	0	0	0	0	1 (4.2)	1 (4.0)	2 (1.4)
Hyperglycaemic Hyper-osmolar Nonketotic Syndrome	0	0	0	0	0	1 (4.0)	1 (0.7)

System Organ Class* / Preferred Term^	Cohort A (N=24) n (%)	Cohort B (N=24) n (%)	Cohort C (N=24) n (%)	Cohort D (N=24) n (%)	Cohort E (N=24) n (%)	Cohort F (N=25) n (%)	Total (N=145) n (%)
Respiratory, Thoracic and Mediastinal Disorders	**1 (4.2)**	**0**	**0**	**0**	**1 (4.2)**	**3 (12.0)**	**5 (3.4)**
Acute Respiratory Failure	0	0	0	0	0	1 (4.0)	1 (0.7)
Dyspnoea	0	0	0	0	1 (4.2)	0	1 (0.7)
Epistaxis	0	0	0	0	0	1 (4.0)	1 (0.7)
Pulmonary Embolism	1 (4.2)	0	0	0	0	0	1 (0.7)
Pulmonary Oedema	0	0	0	0	0	1 (4.0)	1 (0.7)
Respiratory Failure	1 (4.2)	0	0	0	0	0	1 (0.7)
Nervous System Disorders	**0**	**1 (4.2)**	**0**	**1 (4.2)**	**1 (4.2)**	**1 (4.0)**	**4 (2.8)**
Brain Stem Infarction	0	0	0	1 (4.2)	0	0	1 (0.7)
Cerebellar Infarction	0	0	0	0	0	1 (4.0)	1 (0.7)
Subarachnoid Haemorrhage	0	1 (4.2)	0	0	0	0	1 (0.7)
Syncope	0	0	0	0	1 (4.2)	0	1 (0.7)
Injury, Poisoning and Procedural Complications	**0**	**1 (4.2)**	**0**	**1 (4.2)**	**0**	**1 (4.0)**	**3 (2.1)**
Contusion	0	1 (4.2)	0	0	0	0	1 (0.7)
Foreign Body	0	1 (4.2)	0	0	0	0	1 (0.7)
Spinal Fracture	0	0	0	1 (4.2)	0	0	1 (0.7)
Toxicity To Various Agents	0	0	0	0	0	1 (4.0)	1 (0.7)
Ear and Labyrinth Disorders	**0**	**1 (4.2)**	**0**	**0**	**0**	**0**	**1 (0.7)**
Vertigo	0	1 (4.2)	0	0	0	0	1 (0.7)
General Disorders and Administration Site Conditions	**0**	**0**	**0**	**0**	**1 (4.2)**	**0**	**1 (0.7)**
Death	0	0	0	0	1 (4.2)	0	1 (0.7)
Hepatobiliary Disorders	**1 (4.2)**	**0**	**0**	**0**	**0**	**0**	**1 (0.7)**
Cholecystitis	1 (4.2)	0	0	0	0	0	1 (0.7)
Musculoskeletal and Connective Tissue Disorders	**0**	**1 (4.2)**	**0**	**0**	**0**	**0**	**1 (0.7)**
Muscular Weakness	0	1 (4.2)	0	0	0	0	1 (0.7)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	**0**	**0**	**0**	**0**	**1 (4.2)**	**0**	**1 (0.7)**
Colon Cancer[#]	0	0	0	0	1 (4.2)	0	1 (0.7)
Vascular Disorders	**0**	**0**	**0**	**0**	**1 (4.2)**	**0**	**1 (0.7)**
Hypotension	0	0	0	0	1 (4.2)	0	1 (0.7)

* Multiple events within a MedDRA system organ class for the same subject are counted only once when totaled within that system organ class.

^ Multiple events within a MedDRA preferred term for the same subject are counted only once when presented for that MedDRA term.

[#] This subject had a positive fecal occult blood test prior to study entry, but colonoscopy was not performed until Study Week 7 when the subject was diagnosed with adenocarcinoma of the colon with the appearance of an apple-core sized mass. Considering the advanced state of the cancer, the onset of the cancer was likely to pre-date study participation.

Supplemental Table 6: Additional Detail on Deaths that Occurred During the Study*

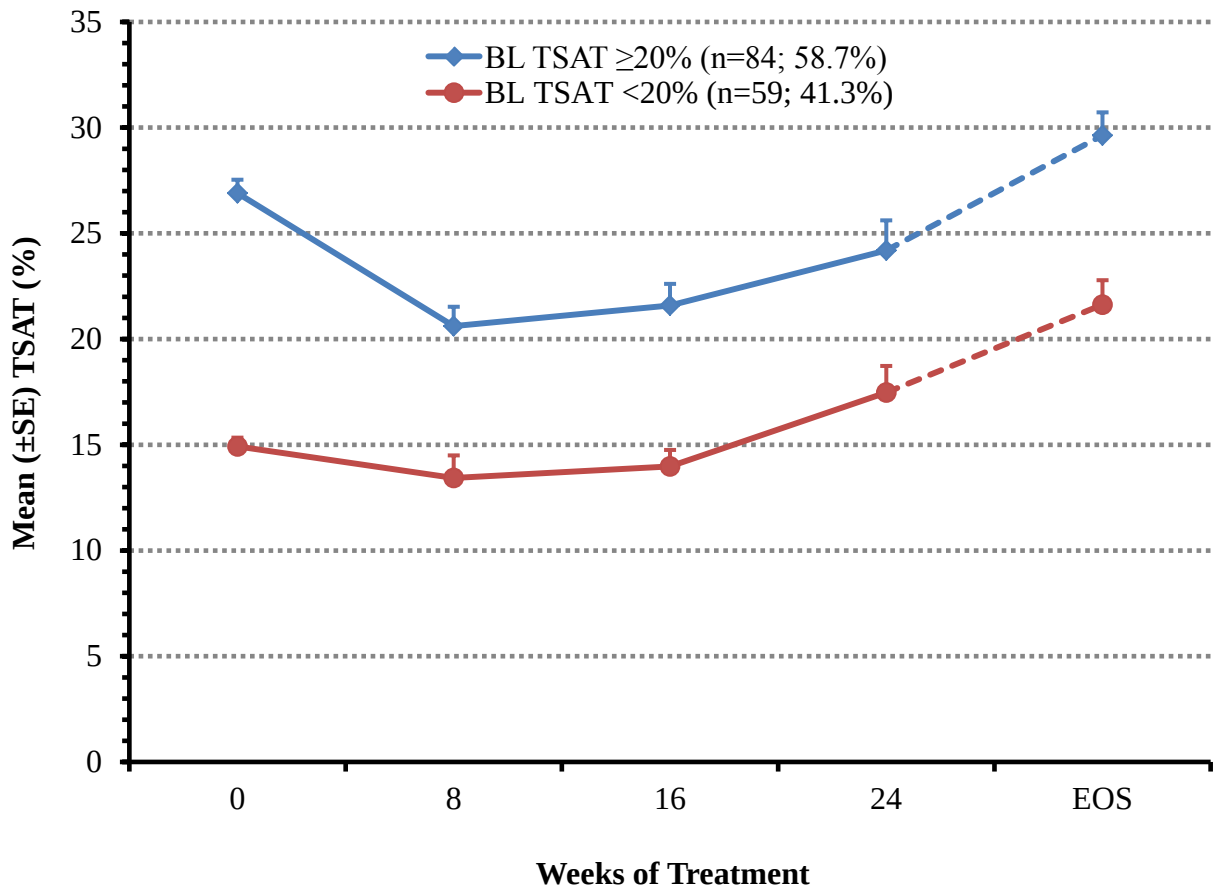
A 68-year-old subject with significant history of coronary artery disease died of a suspected pulmonary embolism while hospitalized for pneumonia, myocardial infarction and respiratory failure.
A 71-year-old subject with a recent history of myocardial infarction and ventricular tachycardia, who died of a cardiopulmonary arrest 3 days after randomization was found to have elevated cardiac bioenzymes (CKD-MB) in blood sampled just prior to first dose of roxadustat.^
A 62-year-old subject with a history of asthma, diabetes, hypertension, and hypothyroidism died unwitnessed in her sleep; the cause of death was attributed to her comorbidities.
A 72-year-old subject with a history of hypertension and chronic obstructive pulmonary disease died of a cardiopulmonary arrest from ischemic heart disease.
A 77-year-old subject with a history of diabetes, coronary artery disease, and hypertension died as a result of a cerebellar infarct, who presented acutely during the follow-up period, more than 2 weeks after uneventful completion of 24 weeks of treatment, and subsequent pulmonary edema, and respiratory failure.

*None of the deaths was considered related to study drug.

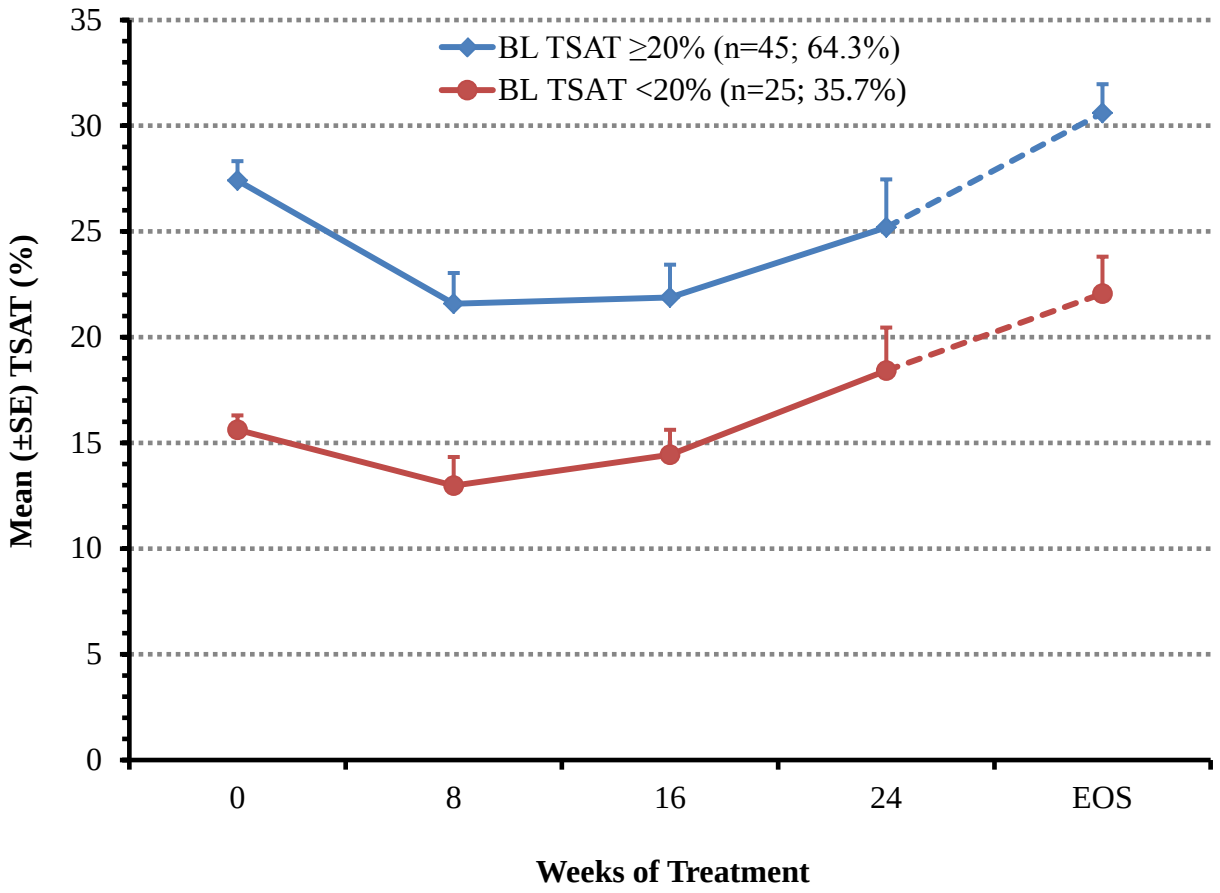
^ This subject was reported to have died on Study Day 3 after taking one dose of roxadustat on Day 1. Retrospectively measured, an elevation of creatine kinase-MB fraction prior to randomization supported the onset of the myocardial infarction prior to initiation of study drug.

Supplemental Figure 1: Iron Parameters Over Time by Subgroup Based on BL Values (EE Population, LOCF)

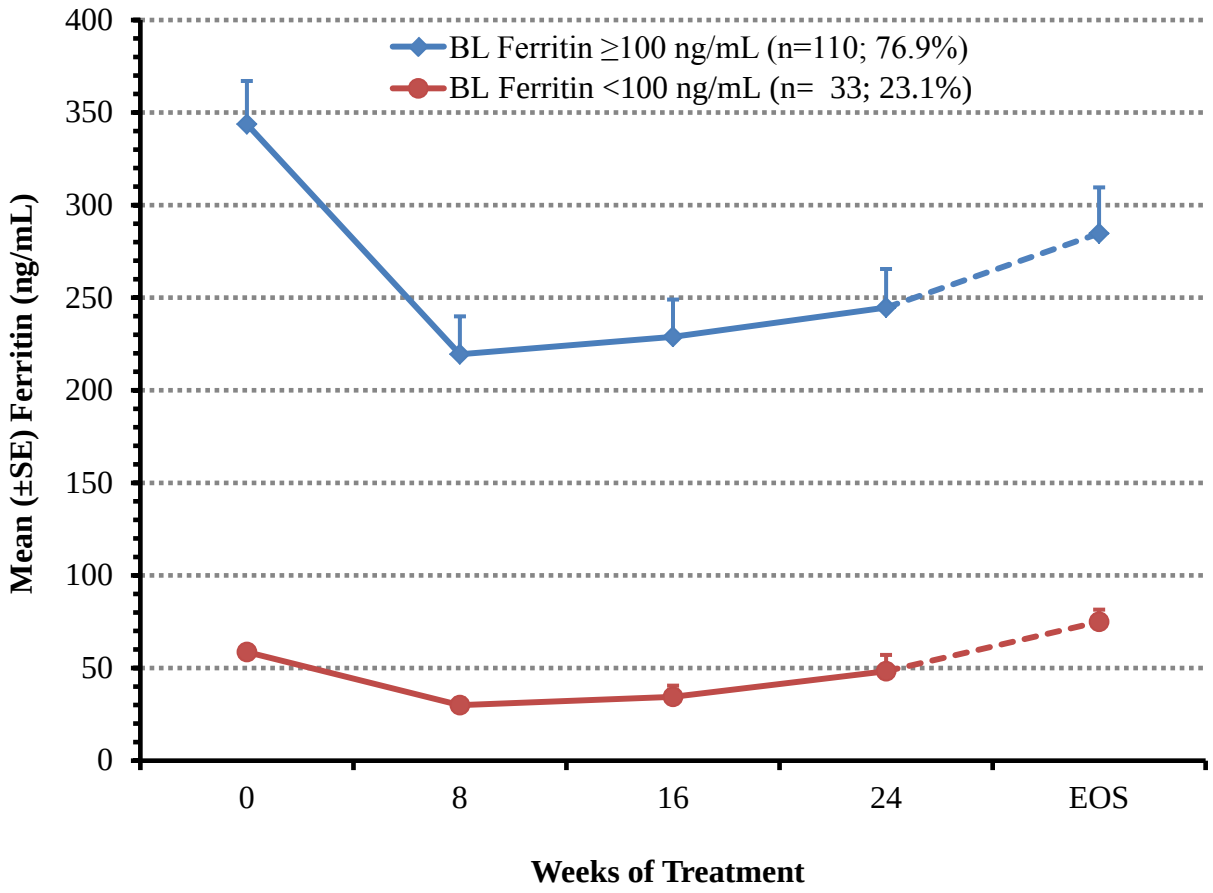
A: TSAT Over Time Among All Cohorts



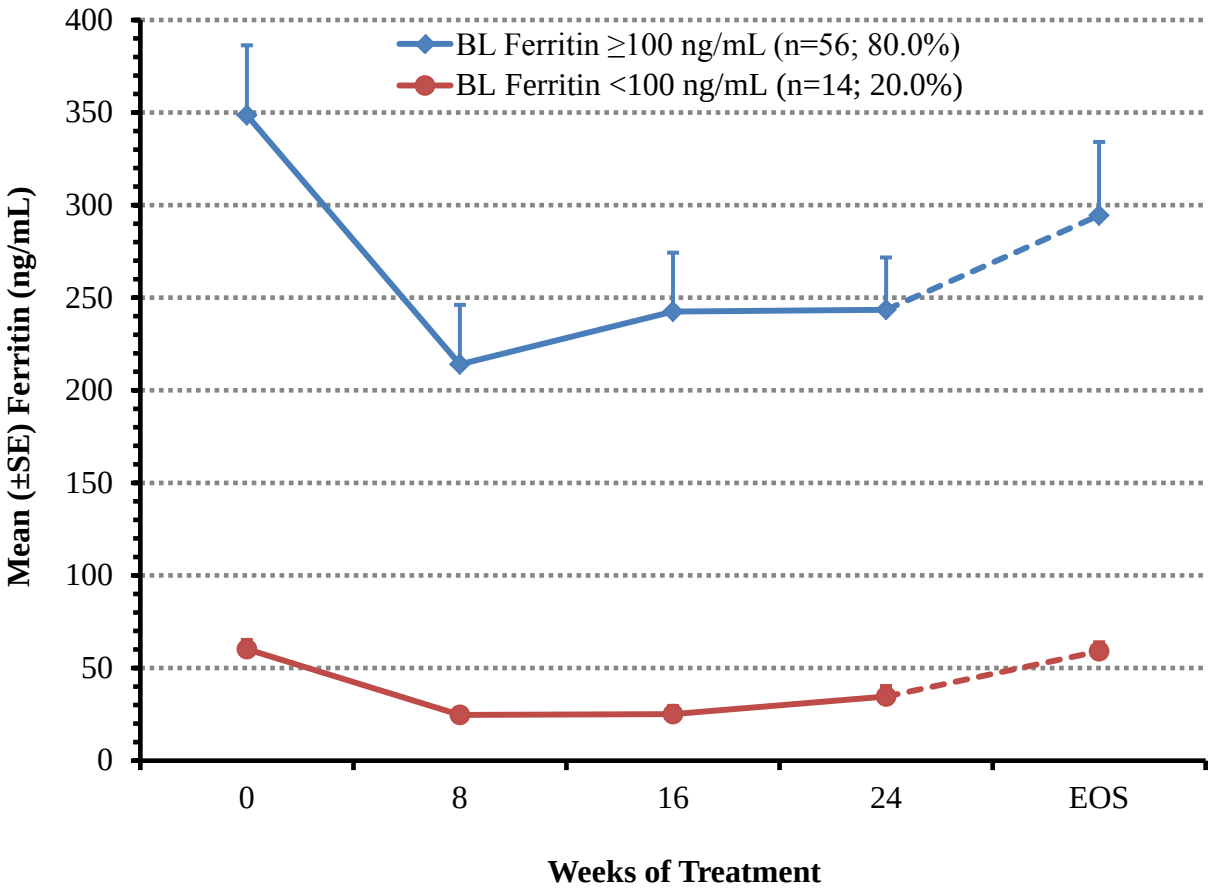
B: TSAT Over Time By Cohort Receiving TIW Dosing (A, C, and D)



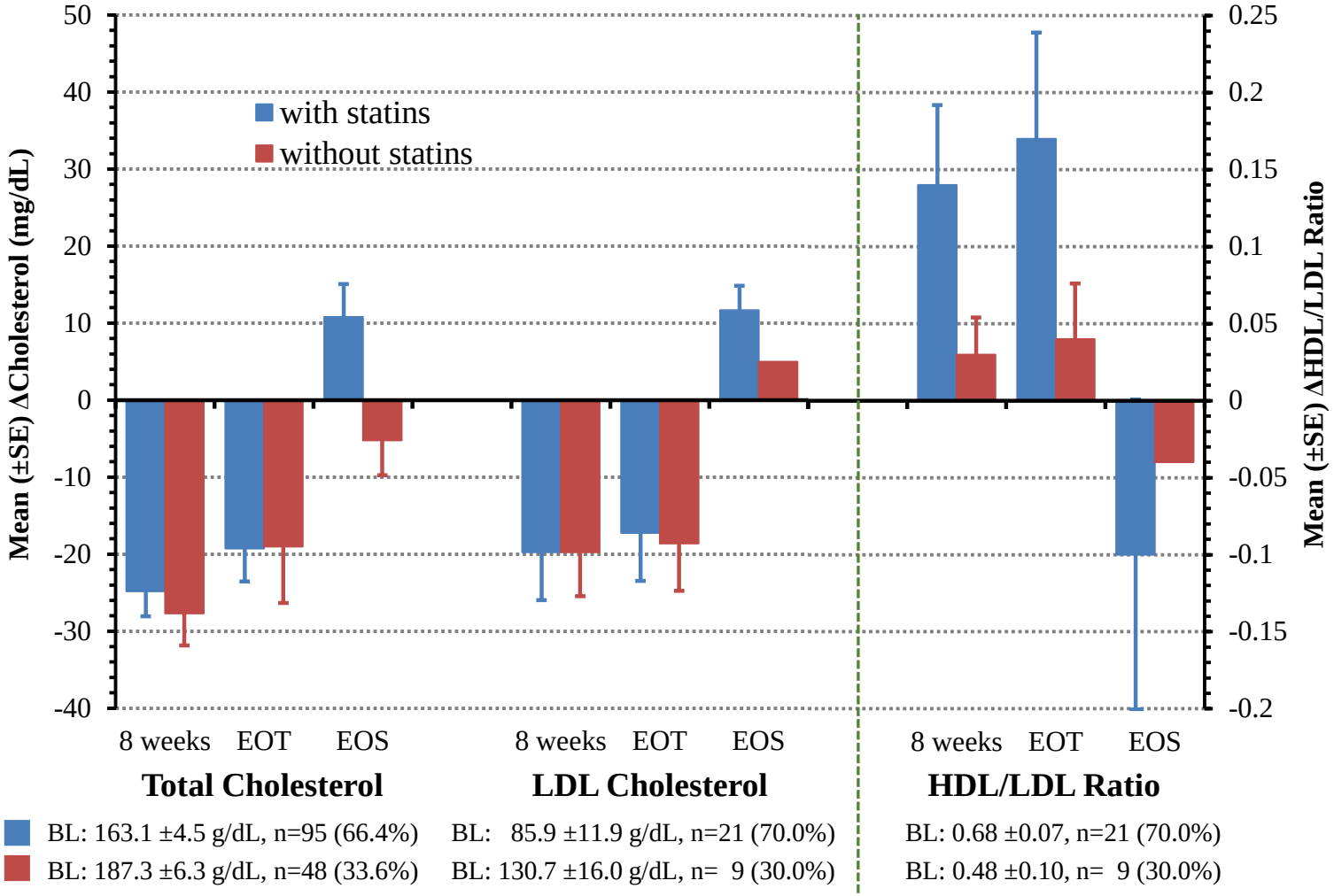
C: Ferritin Over Time Among All Cohorts



D: Ferritin Over Time Among Cohorts Receiving TIW Dosing (A, C, and D)



Supplemental Figure 2: Changes in Mean Total and LDL Cholesterol and HDL/LDL Ratio Among Subjects Receiving and Not Receiving Concomitant Lipid-Lowering Treatment with Statins (Efficacy-Evaluable Population, LOCF)



ΔCholesterol denotes change from baseline in plasma cholesterol.