SIERRAS: A Phase 3, Open-Label, Randomized, Active-Controlled Study of the Efficacy and Safety of Roxadustat in the Maintenance Treatment of Anemia in Subjects with ESRD on Stable Dialysis

FibroGen

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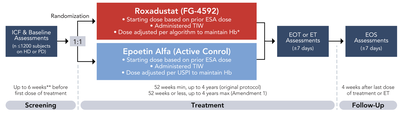
Background

- Roxadustat (FG-4592; ASP1517; AZD9941) is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) that promotes erythropoiesis through increasing endogenous erythropoietin, improving iron regulation, and reducing hepcidin.[1]
- Phase 3 studies conducted in China suggest that roxadustat is efficacious and well tolerated in both dialysis-dependent (DD) and non-dialysis dependent (NDD) chronic kidney disease (CKD) subjects with anemia.[2,3]
- Roxadustat is approved in China to treat anemia associated with chronic kidney disease (CKD) in dialysis-dependent and non-dialysis CKD patients. The drug was approved in Japan September 2019 to treat dialysis dependent patients.
- In this U.S./EU, Phase 3, randomized, open-label, active-controlled trial, the efficacy and safety of roxadustat vs. epoetin alfa was evaluated in dialysis-dependent CKD (DD-CKD) patients who were receiving ESA therapy for anemia.

Methods

Study Design

Figure 1. Study Design



Notes: **EOS** = End of study, **EOT** = End of treatment; **ESA** = Erythropoiesis-stimulating agent; **ET** = Early termination; **HD** = Hemodialysis; **ICF** = Informed consent form; **n** = Number of subjects; **IV** = Intravenous; **PD** = Peritoneal dialysis; **SC** = Subcutaneous; **SmPC** = Summary of product characteristics; **SOC** = Standard of care; **TIW** = Three times a week; **USPI** = US Package Insert; *Maximum roxadustat dose of 3 mg/kg or 400 mg/ week; **For subjects currently taking Mircera®, the screening period can be extended up to 8 weeks.

- FGCL-4592-064 was a multicenter, randomized (1:1), open label, active-controlled Phase 3 study to evaluate the safety and efficacy of roxadustat in the treatment anemia in dialysis dependent subjects receiving ESA therapy.
- Upon randomization subjects discontinued ESA and received oral roxadustat or epoetin alfa three-times a week (TIW).
- Roxadustat dose was adjusted based on a dosing algorithm.
- Epoetin alfa was adjusted per U.S. package insert.
- Oral iron was allowed for all patients; IV iron provided if the physician determined the subject was iron deficient.
- Blood transfusion was allowed as needed.
- ESA rescue was allowed if pre-defined criteria were met, subject was discontinued if 2nd ESA rescue was required.

Dosing Conversion & Algorithm

Table 1. Initial Dosing of Roxadustat (Conversion Table from ESAs to Roxadustat)

Baseline Epoetin (i.e., alfa, beta, theta, zeta, delta, or omega) (IU/week)	Baseline Darbepoetin Alfa (µg/week)	Baseline Mircera® (µg/once monthly)	Converted Day 1 Roxadustat Dosed (mg/dose) TIW
<5,000	<25	<80	70
5,000 to 8,000	25-40	80-120	100
>8,000 to 16,000	>40-80	>120-200	150
>16,000	>80	>200	200

Table 2. Initial Dosing of Epoetin Alfa (Conversion Table from Non-Epoetin ESAs to Epoetin Alfa)

Baseline ESA	Conversion Ratio	Examples of Converted Initial Epoetin Alfa Dose (Approximate) IU/Week
Epoetin (i.e., alfa, beta, theta, zeta, delta, or omega) (IU/week)	× 1	6,000 IU/week × 1 = 6,000 IU/week
Darbepoetin Alfa (µg/week)	× 200	40 µg/week × 200 = 8,000 IU/week
Mircera® (µg/once monthly, i.e., 4 weeks)	× 70 – 80 (for lower Mircera® dose lower conversion ratio may be used)	100 µg/month × 70 = 7,000 IU/week 200 µg/month × 80 = 16,000 IU/week

Key Inclusion Criteria

- Age ≥18 years.
- Receiving dialysis for ≥3 months (original protocol); >2 weeks and <4 months prior to randomization (Amendments 1 & 2).
- Subjects on ESA at least 8 weeks prior to screening (original); at least 4 weeks prior to screening (Amendments 1 & 2).
- Had a mean of recent screening (6-8 weeks prior to randomization) Hb values ≥8.5-12.0 g/dL; with an absolute difference of ≤1.3 g/dL between the highest and the lowest value.
- Iron replete: ferritin>100 and TSAT>20.

References

1. Provenzano et al. *Am J Kid Dis.* 2016;67(6):912-24; 2. Chen et al. *N Engl J Med* 2019; 381:1011-1022; 3. Chen et al. *N Engl J Med* 2019; 381:1001-1010.

Exclusion

- No transfusion <8 weeks (<4 weeks by Amendments 1 & 2).
- No other known causes of anemia.
- Subject had an myocardial infarction, acute coronary syndrome, stroke, seizure, or a thrombotic/thromboembolic event within a major vessel (excluding vascular dialysis access) (e.g., DVT or pulmonary embolism) within 12 weeks prior to randomization.

Primary Efficacy Endpoint

- Change in hemoglobin (Hb) from baseline (BL) to the average level during Weeks 28-52 (for U.S. [FDA]).
  - Non-inferiority (NI) with a lower bound of NI margin of -0.75 g/dL (ITT) [Multiple Imputation (MI) analysis of covariance (ANCOVA) model].
- Change in Hb from BL to the average level during Weeks 28-36, without having received rescue therapy within 6 weeks prior to and during this 8 week evaluation period (for Ex-U.S. [EMA]).
  - NI with a lower bound of NI margin of -0.75 g/dL (PPS, original protocol) [Mixed effect Model Repeat Measurement (MMRM) using baseline value as covariate].

Secondary Efficacy Endpoints (Fixed Sequence Testing)

- Proportion of subjects with hemoglobin level ≥10 g/dL during Week 28-52 (U.S.) / 10-12 g/dL without rescue therapy during Week 28-36 (EU) [non-inferiority].
- Mean change from baseline (CFB) in low density lipoprotein (LDL) cholesterol to the (Weeks 12-28) [superiority].
- Change from baseline to the average Hb level during Weeks 18-24 for patients with baseline hs-CRP >ULN [non-inferiority].
- Average monthly (defined as 4 weeks) IV iron use per subject during Weeks 28-52 [superiority].
- Time to first RBC transfusion during the treatment period [non-inferiority].
- Mean change in pre-dialysis mean arterial pressure (MAP); time to first exacerbation of HT [superiority].

Additional Evaluation of Efficacy

- Mean CFB in iron parameters (serum ferritin, TIBC, TSAT, iron), serum hepcidin, total cholesterol, and LDL/HDL ratio at each scheduled time point up to Week 52.

Demographics & Baseline Characteristics

- 741 patients were randomized (1:1) to receive oral roxadustat (n=370) or epoetin alfa (n=371).
- Roxadustat patients were treated up to 183.7 weeks with average of 1.7 years; epoetin alfa patients were treated up to 180.4 weeks with average of 2.1 years.
- Baseline characteristics were balanced including mean BL Hb levels (10.30 g/dL roxadustat vs. 10.31 epoetin alfa).
- Approximately 98% of patients were iron replete (TSAT >20% and ferritin >100 ng/mL).
- ~40% of patients in each arm >16,000 IU/week epoetin alfa.
- ~95% patients were HD patients at baseline in each arm.

Table 3. Demographics & Baseline Characteristics

	Roxadustat (N=370)	Epoetin Alfa (N=371)
Age, Years		
Mean (SD)	57.6 (13.6)	58.4 (13.3)
18-64	253 (68.4)	246 (66.3)
65-74	80 (21.6)	77 (20.8)
Sex, n (%)		
Male	187 (50.5)	215 (58.0)
Female	183 (49.5)	156 (42.0)
Race, n (%)		
White	165 (44.6)	185 (49.6)
Black	158 (42.7)	156 (42.0)
Asian	21 (5.7)	15 (4.0)
Hispanic/Latino	137 (37.0)	129 (34.8)
Type 2 Diabetes n (%)	241 (65.1)	244 (65.8)
Hb (g/dL), Mean (SD)	9.10 (0.75)	9.09 (0.69)
>10.5 g/dL, n (%)	140 (37.8)	136 (36.7)
≤10.5 g/dL, n (%)	230 (62.2)	235 (63.3)
Mean Baseline ESA Duration (SD)	3.5 (3.24)	3.6 (3.67)
Mean Baseline Dialysis Duration Years (SD)	4.0 (3.47)	3.9 (3.81)
Incident-Dialysis (≥ 4 mo. on dialysis) n (%)	36 (9.73)	35 (9.46)
TSAT (%), Mean (SD)	33.6 (10.1)	33.6 (10.0)
<20% n (%)	10 (2.7)	7 (1.9)
20 - < 40% n (%)	277 (74.9)	278 (74.9)
≥40% n (%)	83 (22.4)	86 (23.2)
Ferritin (ng/mL), Mean (SD)	1002.2 (459.1)	960.8 (414.8)
<100 n (%)	0	1 (0.3)
100 - <400 n (%)	34 (9.2)	34 (9.2)
≥400 n (%)	336 (90.8)	336 (90.6)
CV History, n (%)	229 (61.9)	210 (56.6)
CRP, n (%)		
≤ULN (5.0 mg/L) n (%)	178 (48.1)	192 (51.8)
>ULN (5.0 mg/L) n (%)	189 (51.1)	177 (47.7)
Missing n (%)	3 (0.8)	2 (0.5)

Notes: Hb baseline is defined as the mean of the last 4 last central lab values prior to the first dose; Baseline for CRP, TSAT and ferritin are defined as the mean of values obtained within 6 weeks prior to the first dose.

Results

Primary Endpoints

- Roxadustat met the primary endpoints of change in Hb from baseline to Weeks 28-52 (U.S.) and change in Hb from baseline to Weeks 28-36 censoring rescue (Ex-U.S./EU).

U.S. Primary Endpoint

- Roxadustat met the non-inferiority criteria as the lower bound of 95% CI was above the non-inferiority margin of -0.75 g/dL. Roxadustat also achieved superiority over epoetin alfa as the lower bound of the CI was above 0 (p<0.0001).
- The mean (±SD) Hb CFB averaged over Weeks 28-52 was significantly higher in the roxadustat vs. epoetin alfa-treated subjects, 0.39 (±0.95) g/dL vs. -0.09 (±0.90) g/dL, respectively; LSMean (±SE) [95% CI] of the treatment difference was 0.48 g/dL (±0.06) [0.37, 0.59], p<0.0001.

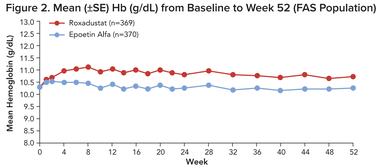
Ex-U.S. Primary Endpoint

- The mean (±SD) Hb CFB averaged over Weeks 28-36 was significantly higher in the roxadustat- vs. epoetin alfa-treated subjects, 0.54 (±1.02) g/dL vs. -0.03 (±0.90) g/dL, respectively; LSMean (±SE) [95% CI] of the treatment difference was 0.55 g/dL (±0.07)[0.40, 0.69], p<0.0001.
- Roxadustat met the non-inferiority criteria as the lower bound of the 95% CI was well above the non-inferiority margin of -0.75 g/dL. Roxadustat also achieved superiority over epoetin alfa, p<0.0001.

Hemoglobin

- Roxadustat-treated subjects maintained stable Hb levels ~11 g/dL.
- Higher proportion of subjects in the roxadustat vs. the epoetin alfa group (66.1% vs. 58.6%, respectively) had mean Hb ≥10 g/dL levels from Weeks 28-52 regardless of receiving rescue therapy.
- Slightly higher proportion of subjects in the roxadustat vs epoetin alfa group (64.1% vs. 60.8%, respectively) had mean Hb from 10-12 g/dL from Weeks 28-36 without having received rescue therapy.

Figure 2. Mean (±SE) Hb (g/dL) from Baseline to Week 52 (FAS Population)

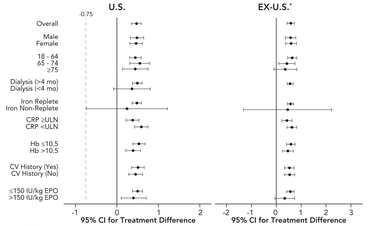


Note: n is the number of subjects with non-missing value at each week.

Subgroup Analysis

- Subgroup analysis consistent with primary efficacy endpoint for U.S. and Ex-U.S. subgroups.
- LSMeans treatment differences favor roxadustat vs. epoetin alfa based on Hb assessment for all patient subgroups analyzed.

Figure 3. Treatment Differences for Hemoglobin CFB by Patient Subgroup

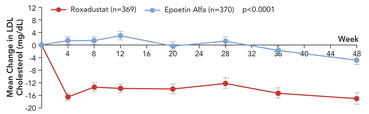


Note: -0.75 gm/dL represents the lower bound for the noninferiority margin.

LDL Cholesterol Over Time

- Roxadustat-treated subjects experienced a consistent decrease in LDL cholesterol from baseline up to Week 52.
- Mean LDL cholesterol levels decreased in the roxadustat group between Weeks 12-28 but increased in the epoetin alfa group (-13.70 mg/dL from baseline of 84.53 (±34.009) vs. 1.23 mg/dL from baseline of 84.45 (±34.124) , respectively).
- The LSMean (±SE) [95% CI] of the treatment difference was -14.67 mg/dL (±1.514) [-17.64, -11.695], (p<0.0001).
- Roxadustat was superior to epoetin alfa (p<0.0001).
- Mean total cholesterol decreased in both treatment groups but was greater in the roxadustat than the epoetin alfa group between Weeks 12-28 (-23.87 mg/dL vs. -1.71 mg/dL, respectively).
- The mean LDL/HDL ratio decreased slightly in the roxadustat group and increased slightly in epoetin alfa group between Weeks 12-28 (-0.09 vs. 0.09, respectively).

Figure 4. Mean (±SE) LDL Cholesterol (mg/dL) CFB to Week 52 (FAS Population)



Note: n is the number of subjects with non-missing value at each week.

Subgroup Analyses by C-Reactive Protein (CRP): Mean Hb Levels and Mean Weekly Dose Requirements

Change in Hemoglobin and Drug Dose Over Time by BL CRP

- **In the roxadustat arm, inflamed patients achieved comparable Hb with comparable dose requirements as non-inflamed.**
- In the epoetin alfa arm, inflamed patients required higher epoetin alfa doses. The mean epoetin alfa dose at Weeks 41-52 is 56% higher than Week 1-4; 82% higher in Year 2.
  - Roxadustat hs-CRP >ULN group maintained Hb with slightly lower than the starting dose vs. epoetin alfa hs-CRP >ULN group required ~50% higher than the starting dose.
  - In subjects with BL hs-CRP >ULN (5.0 mg/dL), the mean change in Hb from BL to Weeks 18-24, was 0.61 g/dL in roxadustat vs. -0.03 g/dL in the epoetin alfa group.
  - Mean treatment difference was 0.69 (95% CI: 0.503, 0.869; p< 0.0001).
  - Roxadustat was non-inferior (lower bound of the 95% CIs was above the NI margin of -0.75) and superior to epoetin alfa in this secondary endpoint (p <0.0001).

Figure 5a. Mean (±SE) Hb from Baseline to Week 52 in Roxadustat-Treated Subjects with hs-CRP ≤ULN or > ULN (FAS)

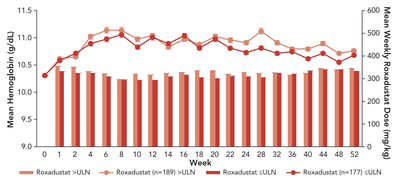
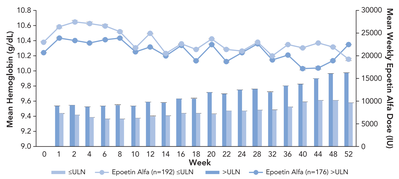


Figure 5b. Mean (±SE) Hb from Baseline to Week 52 in Epoetin Alfa-Treated Subjects with hs-CRP ≤ULN or > ULN (FAS)

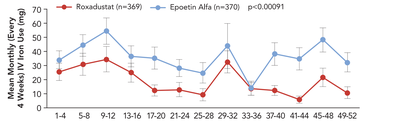


Note: No Ex-U.S. patients who had a history of <4 months dialysis were enrolled in this trial.

Average Monthly IV Iron Use

- Subjects in the roxadustat group received significantly lower mean IV iron per PEM during Weeks 28-52 than subjects in the epoetin alfa group.
- The mean (±SD) monthly IV iron use averaged over Weeks 28-52 was 17.1 mg (±53.4) in the roxadustat arm (n=369) vs. 37.0 mg (±106.8) in the epoetin alfa arm (n=370), p=0.00091.

Figure 6. Mean (±SD) Monthly Total IV Iron Use (FAS)

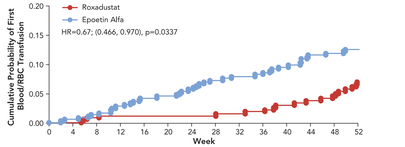


Note: Monthly iron use for each subject = total IV iron in mg / [(last visit date – first drug date +1)/28].

RBC Transfusion

- The time to first RBC transfusion during the treatment period was a secondary endpoint tested for non-inferiority.
- Lower proportion of subjects on roxadustat received a blood transfusion during treatment than the epoetin alfa group (12.5% and 21.1%, respectively).
- Roxadustat was non-inferior (upper bound of 95% CI<1.3, p=0.0307) and superior (HR=0.67; (0.466, 0.970), p=0.0337) to epoetin alfa in this secondary endpoint.

Figure 7. Time to First Blood/RBC Transfusion from Baseline to Week 52 (FAS)



Notes: Time to first occurrence of event is calculated as (first event date or censoring date - first dose date + 1)/7; Subjects were censored at last dose, Week 52+7, last visit date, or death date whichever occurred first, if Blood/RBC, Transfusions over the First 52 Weeks did not occur.

MAP Over Time

- The change in MAP from baseline to averaged over Weeks 20-28 were not significantly different in both treatment groups.
- The mean (±SD) CFB in MAP averaged over Weeks 20-28 was 0.46 (±10.933) mmHg (n=369) in the roxadustat arm vs. 0.04 (±10.489) mmHg (n=370) in the epoetin alfa arm.

Hepcidin & Iron Parameters

Mean CFB serum iron parameters from BL to Week 52

- Mean serum iron and TIBC was increased in the roxadustat arm, while serum ferritin was decreased and TSAT remained the same at 52 weeks
- Roxadustat-treated subjects experienced a greater lowering in serum hepcidin as early as Week 4 that was sustained at Week 52; mean (±SD) CFB -95.53 (148.27) ug/L.

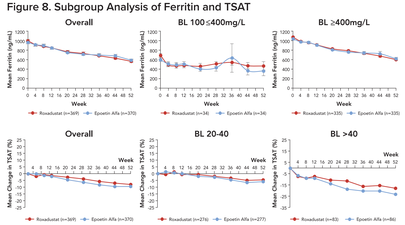
Table 4: Mean Change from Baseline (CFB) in Serum Iron Parameters

	Iron (µg/dL) Mean (SD)	Hepcidin (µg/L) Mean (SD)	TSAT (%) Mean (SD)	Serum Ferritin (ng/mL) Mean (SD)
Roxadustat	-2.12 (36.12)	-95.53 (148.27)	-7.96 (13.70)	-426.46 (340.46)
Epoetin Alfa	-15.64 (28.30)	-66.66 (141.61)	-9.78 (13.07)	-392.75 (338.95)
P-Value	<0.0001	0.0662	0.0341	0.1356

Notes: **TIBC** = total iron-binding capacity, **TSAT** = transferrin saturation; **SD** = standard deviation; Mean CFB in iron parameters and hepcidin analyses were conducted as part of additional efficacy evaluation, not secondary endpoints.

- Reduction in ferritin and TSAT were varied based on baseline levels.

Figure 8. Subgroup Analysis of Ferritin and TSAT



Safety: Adverse Events

- The incidence of overall TEAEs was comparable; 91.6% (339/370) in the roxadustat and 91.4% (338/370) in the epoetin alfa arm.

Table 5. Adverse Event Summary by Preferred Term

Preferred Term	Roxadustat (N=370) n (%)	Epoetin Alfa (N=370) n (%)
Any TEAE	339 (91.6)	338 (91.4)
Any TESAE	242 (65.4)	248 (67.0)
Fatal TESAE	62 (16.8)	58 (15.7)
AEs experienced in ≥5% of subjects in either arm up to 28 Days after the last dose (MedDRA preferred term)		
Nausea	63 (17.0)	60 (16.2)
Hypertension	62 (16.8)	47 (12.7)
Vomiting	60 (16.2)	57 (15.4)
Arteriovenous Fistula Site Complication	58 (15.7)	72 (19.5)
Hyperkalemia	60 (16.2)	56 (15.1)
Dyspnea	56 (15.1)	67 (18.1)
Diarrhea	54 (14.6)	70 (18.9)
Pain in Extremity	49 (13.2)	59 (15.9)
Cough	50 (13.5)	69 (18.6)
Constipation	44 (11.9)	49 (13.2)
Upper Respiratory Tract Infection	43 (11.6)	40 (10.8)
Headache	42 (11.4)	40 (10.8)
Anemia	40 (10.8)	54 (14.6)
Fluid Overload	40 (10.8)	47 (12.7)
Pneumonia	42 (11.4)	52 (14.1)
Hypotension	41 (11.1)	43 (11.6)
Back Pain	39 (10.5)	39 (10.5)
Non-Cardiac Chest Pain	37 (10.0)	41 (11.1)
Arteriovenous Fistula Thrombosis	37 (10.0)	42 (11.4)
Fall	37 (10.0)	58 (15.7)
Acute Myocardial Infarction	34 (9.2)	26 (7.0)
Pyrexia	33 (8.9)	34 (9.2)
Abdominal Pain	33 (8.9)	31 (8.4)
Urinary Tract Infection	32 (8.6)	31 (8.4)
Arteriovenous Graft Thrombosis	31 (8.4)	28 (7.6)
Cardiac Failure Congestive	30 (8.1)	33 (8.9)
Asthenia	27 (7.3)	21 (5.7)
Arthralgia	26 (7.0)	37 (10.0)
Viral Upper Respiratory Tract Infection	26 (7.0)	26 (7.0)
Bronchitis	26 (7.0)	29 (7.8)
Hyperglycemia	25 (6.8)	30 (8.1)
Dizziness	25 (6.8)	30 (8.1)
Cellulitis	25 (6.8)	30 (8.1)
Sepsis	25 (6.8)	27 (7.3)
Oedema Peripheral	23 (6.2)	34 (9.2)
Pruritus	22 (5.9)	21 (5.7)
Tachycardia	20 (5.4)	19 (5.1)
Limb Injury	19 (5.1)	17 (4.6)
Abdominal Pain Upper	19 (5.1)	18 (4.9)
Acute Respiratory Failure	19 (5.1)	29 (7.8)
Atrial Fibrillation	19 (5.1)	26 (7.0)
Peripheral Swelling	18 (4.9)	26 (7.0)
Muscle Spasms	17 (4.6)	25 (6.8)
Coronary Artery Disease	17 (4.6)	22 (5.9)
Syncope	17 (4.6)	21 (5.7)
Anxiety	16 (4.3)	21 (5.7)
Insomnia	15 (4.1)	25 (6.8)
Musculoskeletal Pain	15 (4.1)	20 (5.4)
Pain	15 (4.1)	19 (5.1)
Pleural Effusion	14 (3.8)	24 (6.5)
Bradycardia	14 (3.8)	21 (5.7)
Contusion	14 (3.8)	20 (5.4)
Gastrointestinal Haemorrhage	13 (3.5)	19 (5.1)
Acute Respiratory Failure	12 (3.2)	29 (7.8)
Iron Deficiency	12 (3.2)	23 (6.2)
Angina Pectoris	11 (3.0)	23 (6.2)
Vascular Graft Complication	10 (2.7)	24 (6.5)
Face Oedema	10 (2.7)	19 (5.1)
Pulmonary Edema	7 (1.9)	24 (6.5)

Notes: **AE** = adverse event; **MedDRA** = Medical Dictionary for Regulatory Activities; **SOC** = System Organ Class; **TEAE** = treatment-emergent adverse event; AEs were coded using MedDRA dictionary version 20.0; An AE (classified by preferred term) started during the treatment period was considered a TEAE if it was not present prior to the first dose of study drug, or it was present prior to the first dose of study drug but increased in severity during the treatment period up to 28 days after last dose of study drug or until the administration of another anemia drug (other than the randomized treatment). Subjects with more than one event in a category were counted only once for that category; TEAEs more common in the roxadustat arm are shaded in gray. A TEAE was considered more common in the roxadustat arm if the incidence rate difference between the roxadustat and epoetin alfa-treated subjects was >1%.

Conclusions

- Roxadustat met the U.S. and Ex-U.S. primary efficacy endpoints was both non-inferior and superior to epoetin alfa in Hb change from baseline to Weeks 28-52, and, importantly, roxadustat treatment results in larger Hb increase than epoetin alfa in the subgroup of patients with inflammation (elevated CRP) and those hyporesponsive to ESA (with high baseline ESA dose).
- Roxadustat significantly reduced mean LDL cholesterol levels.
- Roxadustat subjects required less IV iron than epoetin alfa-treated subjects to maintain higher Hb levels, while TSAT levels remain comparable between the two arms throughout. This supports the thesis of roxadustat as a HIF-PHI has a favorable impact on iron mobilization towards coordinated erythropoiesis, and is differentiated from erythropoietin analogues like epoetin alfa.
- Roxadustat lowers the risk of RBC transfusions by 33% in comparison to epoetin alfa (active control SOC), with HR (95%CI) of 0.67 (0.466, 0.970), p=0.0337.
- Roxadustat was equally efficacious in inflamed and non-inflamed subjects; dose requirements of roxadustat were similar in inflamed and the non-inflamed patients while achieved comparable Hb levels. In contrast, higher epoetin doses were required in inflamed patients than the non-inflamed.
  - Roxadustat effect is durable over time as the average dose requirement remain fairly stable; in contrast, dose requirement increased over time in the epoetin alfa treated patients.
- Overall, TEAEs and TESAEs were balanced between the roxadustat and epoetin alfa groups and were generally consistent with those typically expected in study patient population of ESRD on chronic dialysis therapy.
- No safety signal was identified in this study and roxadustat was found to be safe for long-term use to maintain Hb in dialysis dependent patients.