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

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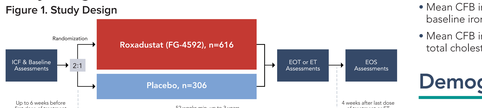
Background

- 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]
- 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 Phase 3, randomized, double-blind, placebo-controlled trial, the efficacy and safety of roxadustat vs. placebo was evaluated in patients with CKD (stages 3, 4 or 5) who were not dialysis-dependent (NDD-CKD).
- This is a unique Phase 3 study design comparing roxadustat to placebo in contrast to other ongoing HIF-PHI Phase 3 studies with erythropoiesis stimulating agent (ESA) comparators.

Methods

Study Design

Figure 1. Study Design



Notes: **EOS** = End of study; **EOT** = End of treatment; **ET** = Early termination; **ICF** = Informed consent form; *n* = Number of subjects; **TIW** = Three times a week.

- FGCL-4592-060 was a multicenter, randomized (2:1), double-blind, placebo-controlled Phase 3 study to evaluate the safety and efficacy of roxadustat in the treatment of anemic subjects with Stage 3-5 CKD who were not on dialysis at the time of randomization.

Dosing

- **Oral Therapy:** Subjects received oral roxadustat (n=616) or placebo (n=306) three-times weekly (TIW).
- **Initial Dosing:** Three-times a week (TIW) frequency using a tiered, weight-based starting dose.
- **Correction Phase:** Subjects were dosed according to dosing algorithm to achieve a hemoglobin (Hb) level 11.0 g/dL and 1.0 g/dL increase from baseline (BL).
- **Maintenance Phase:** Subjects continued dosing per algorithm to maintain Hb values after initial correction; roxadustat doses were adjusted according to Hb levels every four weeks.

Study Drug Dosing

Roxadustat Dosing: Oral, Thrice-Weekly (3x/week)*

- **Starting Dose:** 70 mg TIW (body weight 45 - <70 kg); 100 mg TIW (70-160 kg).

Table 1. NDD Roxadustat Maintenance Dose Adjustment Rules (Assessed Every 4 Weeks with Treatment Goal of Hb 11 g/dL (+/-1 g/dL)

Changes in Hb Over Past 4* Weeks	Hb <10.5 g/dL	Hb 10.5 to 11.9 g/dL	Hb 12.0 to 12.9 g/dL	Hb ≥13.0 g/dL
<-1.0	↑	↑	No change	Dose withheld and resumed when Hb was <12 g/dL, at a dose that was to be reduced by two dose steps
-1.0 to 1.0	↑	No change	↓	
>1.0	No change	↓	↓	

- **Roxadustat Dose Steps:** 20, 40, 50, 70, 100, 150, 200, 250, & 300 mg.
- **NDD Comparator:** Matching placebo, dosing adjustment rules same as roxadustat.

* subset of patients dosed BIW (n=63) or QW (n=63) during Hb maintenance.

Key Inclusion Criteria

- Age ≥18 years.
- Diagnosis of Stage 3-5 CKD, not receiving dialysis, with eGFR <60 mL/min/1.73m².
- Baseline Hb ≤10.0 g/dL.
- Ferritin ≥30 ng/mL.
- TSAT ≥5%.

Key Exclusion Criteria

- Any ESA treatment within 12 weeks prior to randomization.
- More than one dose of IV iron within 12 weeks prior to randomization.
- RBC transfusion within 8 weeks prior to randomization.
- Myocardial infarction, acute coronary syndrome, stroke, seizure, or a thromboembolic event (e.g., deep vein thrombosis or pulmonary embolism) within 12 weeks prior to randomization.

Primary Efficacy Endpoint

- Change in Hb from BL averaged over Weeks 28-52 (for U.S. [FDA]).
- Proportion of subjects who achieve an Hb response at two consecutive visits during the first 24 weeks of treatment without rescue therapy (for EU [EMA]).
  - A Hb response was defined, using central laboratory values, as the following: Hb ≥11.0 g/dL and Hb increase from BL by ≥1.0 g/dL in subjects with BL Hb >8.0 g/dL, or an increase in Hb by ≥2.0 g/dL in subjects with BL Hb ≤8.0 g/dL.

Key Secondary Efficacy Endpoints

- Mean change from baseline (CFB) in Hb averaged over Weeks 28-36 with censoring for rescue therapy.
- Mean CFB in low-density lipoprotein (LDL) cholesterol averaged over Weeks 12-28.
- Time to rescue therapy in the first 52 weeks of treatment.
- Time to blood/RBC transfusion in the first 52 weeks of treatment.

Additional Efficacy Endpoints

- Mean CFB in Hb averaged over Weeks 28-36 regardless of rescue therapy by baseline iron status.
- 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

- 922 patients were randomized (2:1) to receive oral roxadustat (n=616) or placebo (n=306).
- Baseline characteristics were well balanced including BL Hb levels that averaged 9.1 g/dL in both arms.
- Treatment duration was up to 4.5 years; the median duration of study drug exposure was 95.6 weeks for roxadustat-treated subjects vs 52.1 weeks for placebo-treated subjects.
- The average eGFR was 21.9 and 22.4 ml/min in the roxadustat and placebo arms with approximately 32% of patients having stage 5 CKD at BL.
- Approximately 40% of patients were not iron replete as defined by TSAT <20% or ferritin <100 ng/mL.
- Approximately 25% of patients were inflamed as defined by a CRP greater than the upper limit of normal.

Table 2. Demographics & Baseline Characteristics

	Roxadustat (N=616)	Placebo (N=306)
Age, Years*		
n	616	306
Mean (SD)	64.9 (12.6)	64.8 (13.2)
Median	66	66
Min, Max	(22, 94)	(22, 91)
Age Group, n (%)		
18–64	271 (44.0)	146 (47.7)
65–74	192 (31.2)	79 (25.8)
≥75	153 (24.8)	81 (26.5)
Sex, n (%)		
Male	241 (39.1)	130 (42.5)
Female	375 (60.9)	176 (57.5)
Hb (g/dL), Mean (SD)	9.10 (0.75)	9.09 (0.69)
≤8 g/dL, n (%)	52 (8.4)	23 (7.5)
>8 - ≤9 g/dL, n (%)	173 (28.1)	97 (31.7)
>9 g/dL, n (%)	391 (63.5)	186 (60.8)
eGFR (mL/min/1.73 m²), Mean (SD)	21.9 (11.5)	22.4 (11.4)
<10, n (%)	71 (11.5)	19 (6.2)
10 - <15, n (%)	124 (20.1)	76 (24.8)
15 - <30, n (%)	292 (47.4)	146 (47.7)
30 - <45, n (%)	96 (15.6)	46 (15.0)
45 - <60, n (%)	31 (5.0)	18 (5.9)
≥60, n (%)	2 (0.3)	1 (0.3)
TSAT (%), Mean (SD)	26.4 (10.9)	26.2 (11.3)
<20%	169 (27.4)	95 (31.0)
20 - ≤40%	375 (60.9)	174 (56.9)
≥40%	69 (11.2)	35 (11.4)
Missing	3 (0.5)	2 (0.7)
Ferritin (ng/mL), Mean (SD)	308.6 (388.3)	308.4 (352.5)
<100	151 (24.5)	88 (28.8)
100 - <400	321 (52.1)	141 (46.1)
≥400	142 (23.1)	76 (24.8)
Missing	2 (0.3)	1 (0.3)
Iron Repletion Status, n (%)		
Ferritin ≥100 ng/mL and TSAT ≥20%	373 (60.6)	170 (55.6)
Ferritin <100 ng/mL or TSAT <20%	241 (39.1)	134 (43.8)
Missing	2 (0.3)	2 (0.7)
CRP, n (%)		
≤ULN (4.9 mg/L)	457 (74.2)	223 (72.9)
>ULN (4.9 mg/L)	156 (25.3)	81 (26.5)
Missing	3 (0.5)	2 (0.7)

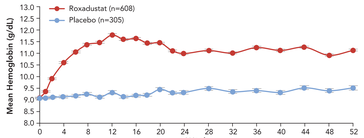
Notes: Baseline Hb is defined as the mean of up to four last central lab values prior to the first dose; Baseline for CRP, TSAT and ferritin are defined as the mean of values obtained within 2 weeks prior to the first dose; eGFR baseline is defined as the mean of all available central lab values prior to the first dose of study drug including the day 1 pre-dose value.

Results

Change in Hemoglobin Over Time

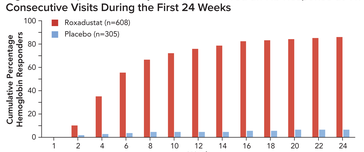
- **Primary Efficacy Endpoint (for U.S. [FDA]):** The mean (±SD) Hb CFB averaged over weeks 28-52 was significantly higher in the roxadustat- vs. placebo-treated subjects, 2.00 (±0.952) g/dL vs. 0.16 (±0.895) g/dL, respectively; LSMean (±SE) [95% CI] of the treatment difference was 1.85 g/dL (±0.059)[1.735, 1.968], p<0.0001. (Fig 2a).
- **Primary Efficacy Endpoint (for EU):** The proportion of subjects who achieved an Hb response at two consecutive visits during the first 24 weeks of treatment was significantly higher in the roxadustat- vs. placebo-treated subjects, 86.0% (95% CI: 83.0%, 88.7%) vs. 6.6% (95% CI: 4.1%, 9.9%), p <0.0001. (Fig 2b).
- **Secondary Efficacy Endpoint:** The mean (±SD) CFB in Hb, averaged over Weeks 28-36 with censoring for rescue therapy was 2.02 (±1.067) g/dL (n=520) in the roxadustat arm vs. 0.20 (±0.994) g/dL (n=219) in the placebo arm; LSMean (±SE) [95% CI] of the treatment difference was 1.88 g/dL (±0.078) [1.730, 2.037], p<0.0001.

Figure 2a. Change in Mean (±SE) Hb (g/dL) from Baseline to Week 52



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

Figure 2b. Proportion of Subjects Who Achieved an Hb Response at Two Consecutive Visits During the First 24 Weeks



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

Hemoglobin Change by Subgroup

- The results of all subgroup analyses were consistent with the results of the primary analysis.

Figure 3a. Hb Response by Subgroup: Change in Hb from BL Averaged Over Weeks 28-52

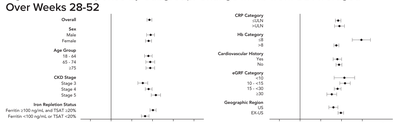
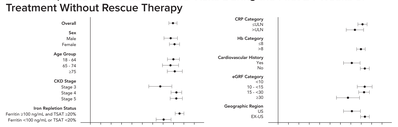


Figure 3b. Hb Response by Subgroup: Proportion of Subjects Who Achieve an Hb Response at Two Consecutive Visits During the First 24 Weeks of Treatment Without Rescue Therapy



Note: Hb response is defined, using central laboratory values, as: Hb ≥11.0 g/dL and a Hb increase from BL ≥1.0 g/dL in subjects with BL Hb >8.0 g/dL, or an increase in Hb ≥2.0 g/dL in subjects with BL Hb ≤8.0 g/dL.

CFB in Hemoglobin by Baseline Iron Status

- The mean (±SD) CFB in Hb averaged over Weeks 28-36 in the roxadustat arm was 2.07 (±1.03) g/dL (n=241) in subjects with BL ferritin<100 ng/mL or TSAT <20% vs. 1.99 (±1.04) g/dL (n=366) in subjects with BL ferritin ≥100 ng/mL and TSAT ≥20%.
- Both of these results were significantly higher (p<0.0001) than corresponding placebo-treated subjects who experienced a mean (±SD) CFB of 0.37 (±1.05) g/dL (n=134) and -0.02 (±0.88) g/dL (n=170), respectively.

Table 3. Mean (±SD) CFB in Hb (g/dL) Averaged Over Weeks 28-36 Regardless of Rescue Therapy in Subjects by Baseline Iron Status (FAS Population)

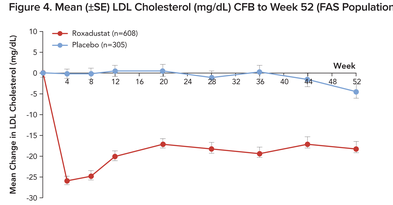
	Roxadustat		Placebo			
	Hb Values (Observed + Imputed)	Hb Change from Baseline	Hb Values (Observed + Imputed)	Hb Change from Baseline	Treatment Difference[b]	P-Value
Baseline Ferritin ≥100 ng/mL and TSAT ≥20%, n	**366**	**366**	**170**	**170**	**—**	**—**
Baseline*	9.07 (0.74)	—	9.05 (0.72)	—	—	—
Weeks 28-36	11.06 (0.87)	1.99 (1.04)	9.03 (1.04)	-0.02 (0.88)		
LSMean (SE)	—	1.98 (0.053)	—	-0.05 (0.077)	2.03 (0.088)	<0.0001
95% CI	—	(1.873, 2.082)	—	(-0.204, 0.097)	(1.859, 2.202)	—
Baseline Ferritin <100 ng/mL or TSAT <20%, n	**241**	**241**	**134**	**134**	**—**	**—**
Baseline	9.12 (0.76)	—	9.12 (0.66)	—	—	—
Weeks 28-36	11.20 (0.90)	2.07 (1.03)	9.49 (1.18)	0.37 (1.05)	—	—
LSMean (SE)	—	2.10 (0.068)	—	0.39 (0.091)	1.71 (0.108)	<0.0001
95% CI	—	(1.969, 2.236)	—	(0.213, 0.571)	(1.498, 1.923)	—

Notes: Hb values under the influence of a rescue therapy were not censored in the analysis. The intermittent missing hemoglobin data were imputed for each treatment relying on non-missing data from all subjects within each treatment group using MCMC imputation model. Monotone missing data were imputed by regression from its own treatment group. Baseline Hb is defined the mean of up to four last central lab values prior to the first dose of study treatment; *Baseline Hb is defined as the mean of up to four last central lab values prior to the first dose of study treatment; †Treatment comparison was made using the multiple imputation strategy by combining the results of ANCOVA model with baseline Hb and baseline eGFR as covariates , and treatment and other randomization stratification factors, except baseline Hb (≥8 g/dL vs. <8 g/dL) and eGFR (<30 vs. ≥30 mL/min/1.73m2), as fixed effects.

LDL Over Time

- The LDL cholesterol lowering effect of roxadustat manifested at Week 4 and was sustained up to Week 52. (Fig 4).
- The mean (±SD) CFB in LDL cholesterol, averaged over Weeks 12-28 was -18.48 (±29.60) mg/dL (18.9% reduction from baseline mean of 97.74 mg/dL) (n=564) in the roxadustat arm vs. 0.22 (±29.37) mg/dL (n=269) in the placebo arm (baseline mean of 96.39 mg/dL). The LSMean (±SE) [95% CI] of the treatment difference between the two arms was -17.26 mg/dL (±1.73) [-20.65, -13.87]; p<0.0001. Subgroup analyses of subjects with or without use of concomitant statin therapy were consistent with the overall population.
- In addition, total cholesterol (TC) and LDL/HDL ratio were reduced over time. The mean (±SD) CFB to Week 52 in TC was -27.20 mg/dL (45.79) from baseline mean of 174.56 mg/dL for roxadustat arm vs. -3.21 (49.78) from baseline mean of 172.59 for placebo arm. For LDL/HDL ratio, both arms had baseline ratio of 2.23; the mean (±SD) CFB to Week 52 was -0.19 (0.91) for roxadustat vs. -0.10 (0.79) for placebo.
- Mean CFB in TC and LDL/HDL ratio analyses were conducted as part of additional efficacy evaluation, not secondary endpoints.

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

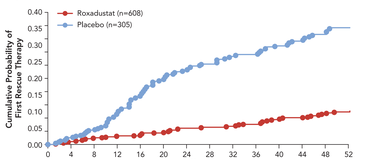


Note: *n* is the number of subjects with non-missing value at each week.

Time to Rescue Rx and Blood/RBC Transfusion

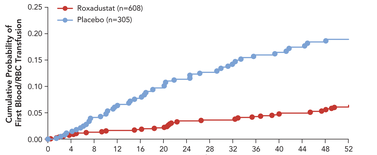
- The proportion of subjects who received any rescue therapy (blood/RBC transfusion, ESA use, and IV iron) in the first 52 weeks of treatment was 8.9% in the roxadustat arm vs. 28.9% in the placebo arm; HR 0.19 (95% CI: 0.138, 0.276), p <0.0001.
- The proportion of subjects who received blood/RBC transfusion in the first 52 weeks of treatment was 5.6% in the roxadustat arm vs. 15.4% in the placebo arm; HR 0.26 (95% CI: 0.165, 0.406), p <0.0001 (nominal).

Figure 5a. Time to Rescue Therapy from Baseline to Week 52



Notes: Rescue therapy: *Any use of RBC transfusion, ESA, or IV iron*; From a Cox Proportional hazards model adjusting for BL Hb, baseline eGFR and other randomization stratification factors, except BL Hb (≥8 g/dL vs. <8 g/dL) and eGFR (<30 vs. ≥30 mL/min/1.73m²); 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, last visit date, or death date whichever occurred first, if rescue therapy over first 52 weeks did not occur.

Figure 5b. Time to First Blood/RBC Transfusion from Baseline to Week 52



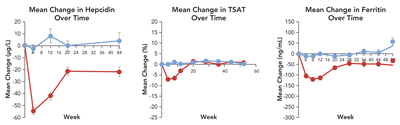
Notes: From a Cox Proportional hazards model adjusting for BL Hb, baseline eGFR and other randomization stratification factors, except BL Hb (≥8 g/dL vs. <8 g/dL) and eGFR (<30 vs. ≥30 mL/min/1.73m²); Time to first occurrence of event is calculated as (first event date or censoring date - first dose 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.

Hepcidin & Iron Parameters

Mean CFB Serum Iron Parameters from BL to Week 52

- Roxadustat-treated subjects experienced a lowering in serum hepcidin at Week 4, and this lowering effect was sustained at Week 44. The mean (±SD) CFB to Week 44 was -22.11 (80.899) µg/L from baseline mean of 110.66 µg/L in the roxadustat arm vs. 3.88 (80.927) µg/L in the placebo arm (baseline mean of 106.11 µg/L). The LSMean (±SE) [95% CI] of the treatment difference between the two arms was -25.71 µg/L (±6.526) [-38.523, -12.903].
- Mean serum TSAT initially decreased from baseline up to Weeks 4-8 in the roxadustat arm and then gradually increased and plateaued after Week 20, while mean TSAT remained approximately constant in the placebo arm. Mean serum ferritin values decreased from baseline up to Week 52 in the roxadustat arm, while mean serum ferritin levels remained approximately constant in the placebo arm.

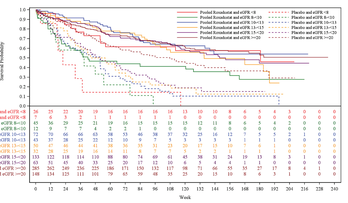
Figure 6. Effect of Roxadustat on Key Iron Parameters



Treatment Duration By Baseline eGFR

- The risk of morbidity and mortality are inversely related to BL eGFR among patients with CKD prior to initiating dialysis (USRDS 2016, Chapter 3).
- In this study, subjects in the roxadustat arm had a substantially higher overall study drug exposure compared to subjects in the placebo arm; the differential dropout between roxadustat and placebo arms begins to manifest as early as Week 8.
- For each BL eGFR category, study drug discontinuation was higher in the placebo arm compared to roxadustat arm, and the relative difference in discontinuation rates was especially pronounced in the lowest baseline eGFR category.
- Among patients with eGFR <10 mL/min/1.73 m² at BL, approximately 45% of placebo-treated subjects dropped out of study 6 months after randomization.
- Due to potential bias in adverse event reporting resulting from differential exposure between roxadustat and placebo arms, safety assessment includes 100 patient-exposure years (100 PEY) as well as treatment-emergent adverse events up to 52 weeks.

Figure 7. Proportion of Subjects on Treatment Over Time by Baseline eGFR Category (Safety Population)



Safety

- When compared through 52 weeks, the incidence of overall TEAEs was comparable; 87.6% (n=535) in the roxadustat and 85.9% (262) in the placebo arm.
- When compared through 52 weeks, the incidence of overall TESAEs was comparable; 33.2% (n=611) in the roxadustat and 29.8% (n=305) in the placebo arm.
- In addition, time-to-death analyses at various timepoints (52 weeks, 104 weeks, up to 28 days after the last dose of study drug, and including deaths during LTFU) suggest there was no significant difference in mortality risk between the two arms.

Table 4. Adverse Event Summary by Preferred Term

	Roxadustat (N=611)		Placebo (N=305)	
Preferred Term	**n (%)**	**PEY=527.3 Events (Event Rate per 100 PEY)**	**n (%)**	**PEY=230.9 Events (Event Rate per 100 PEY)**
TEAEs	**535 (87.6)**	**3393 (643.4)**	**262 (85.9)**	**1579 (684.0)**
TESAEs	**203 (33.2)**	**395 (74.9)**	**91 (29.8)**	**169 (73.2)**
Death*	**58 (9.5)**	**58 (4.4)**	**24 (7.9)**	**24 (4.5)**
AEs experienced in ≥5% of subjects in either treatment arm [Week 52] (MedDRA preferred term)				
Nausea	71 (11.6)	81 (15.4)	24 (7.9)	26 (11.3)
Hyperkalemia	70 (11.5)	93 (17.6)	32 (10.5)	36 (15.6)
Constipation	70 (11.5)	85 (16.1)	29 (9.5)	32 (13.9)
Hypertension	68 (11.1)	82 (15.5)	24 (7.9)	29 (12.6)
Viral upper respiratory tract infection	66 (10.8)	89 (16.9)	30 (9.8)	39 (16.9)
Edema peripheral	66 (10.8)	88 (16.7)	20 (6.6)	28 (12.1)
Upper respiratory tract infection	58 (9.5)	84 (15.9)	39 (12.8)	46 (19.9)
Diarrhea	50 (8.2)	56 (10.6)	26 (8.5)	32 (13.9)
Headache	45 (7.4)	61 (11.6)	24 (7.9)	27 (11.7)
Urinary tract infection	43 (7.0)	59 (11.2)	23 (7.5)	39 (16.9)
Dizziness	40 (6.5)	47 (8.9)	25 (8.2)	28 (12.1)
Insomnia	39 (6.4)	42 (8.0)	7 (2.3)	7 (3.0)
Vomiting	38 (6.2)	46 (8.7)	19 (6.2)	19 (8.2)
Pruritus	37 (6.1)	45 (8.5)	17 (5.6)	21 (9.1)
Cough	36 (5.9)	42 (8.0)	22 (7.2)	24 (10.4)
End stage renal disease	36 (5.9)	36 (6.8)	15 (4.9)	15 (6.5)
Back pain	35 (5.7)	41 (7.8)	13 (4.3)	14 (6.1)
Hypoglycemia	33 (5.4)	38 (7.2)	7 (2.3)	8 (3.5)
Arthralgia	32 (5.2)	35 (6.6)	19 (6.2)	21 (9.1)
Dyspnoea	22 (3.6)	29 (5.5)	19 (6.2)	22 (9.5)
Anemia	7 (1.1)	7 (1.3)	38 (12.5)	46 (19.9)

Notes: An AE (classified by PT) occurred after the first dose of study drug through week 52 of dosing 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 double-blind treatment period; An AE that occurred after the last dose of study drug wasn't counted as a TEAE; Patient-Exposure-Year (PEY) = (Last Dose Date - First Dose Date + 1)/365.25; *Deaths reported for the long-term follow-up analysis of the safety population (PEY=1303.4 for roxadustat and 532.9 for placebo).

Conclusions

- This study included patients with more advanced CKD, more severe anemia, and less iron repletion at baseline, than historical studies in CKD anemia.
- Roxadustat met both primary efficacy endpoints: Hb change (U.S. FDA) and % Hb responders (EU EMA).
- Roxadustat was superior to placebo increasing Hb in the treatment of anemia with a significantly higher proportion of subjects achieving a Hb response in this non-dialysis CKD population.
- Roxadustat reduced the risk of rescue therapy and blood/RBC transfusion compared to placebo.
- Roxadustat is effective regardless of iron-repletion status.
- The overall exposure-adjusted safety profile of roxadustat observed during this study was comparable with placebo and consistent with that expected in the CKD study population.