An Open-Label Extension Study to Evaluate the Efficacy and Safety of Roxadustat for the Long-Term Maintenance Treatment of Anemia in Dialysis and Non-Dialysis Patients with Chronic Kidney Disease

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]
- The clinical data from prior 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]
- In this open-label, extension study, subjects with dialysis-dependent (DD-CKD) and non-dialysis-dependent chronic kidney disease (NDD-CKD) who have completed the treatment period of a phase 2 roxadustat anemia study in the U.S. were enrolled and treated with roxadustat.

Methods

Study Design

- Single-arm, multicenter, open-label, extension study to evaluate the long-term efficacy and safety of roxadustat in the maintenance of hemoglobin (Hb) in DD-CKD and NDD-CKD subjects.
- Subjects who received roxadustat in a previous study continued to receive roxadustat at the same dose and dosing frequency (TIW, BIW, or QW) as they received at the end of their last study, unless a dose adjustment was required.

Key Inclusion Criteria

- Age ≥18 years.
- Subjects who have completed the treatment period of an ongoing Phase 2 roxadustat anemia study in the U.S.

Key Exclusion Criteria

- Subjects assigned to epoetin alfa in a previous ongoing Phase 2 roxadustat anemia study.
- Subjects who received roxadustat in a previous study that did not demonstrate adequate Hb response per the investigator's clinical judgment.

Efficacy Endpoints Presented

- Mean monthly Hb values over time.
- Roxadustat weekly total doses over time.
- Dose adjustment frequencies.
- Results presented here are based on interim data as database lock has not yet occurred.

Safety Endpoints

- Safety and tolerability were assessed by adverse events, vital signs, electrocardiogram findings, and clinical laboratory values.

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.

Demographics & Baseline Characteristics

- Fifteen subjects with NDD-CKD (n=14) and DD-CKD (n=1) were enrolled and treated.
- Mean age was 64.6 years; [range, 38-79 years], 66.7% (10/15) were female, 86.7% (13/15) were white.
- Baseline Hb levels averaged 10.05 g/dL; [range, 8.3-11.2 g/dL], and was likely affected by the mean time between participation in the prior protocols and entry into this study of 112.0 days (min: 8 days, max: 178 days).
- eGFR averaged 26.1 mL/min; [range, 7.3-48.2 mL/min].

Table 1. Demographics & Baseline Characteristics (All Subjects)

		Roxadustat N=15
Age (year)	n	15
	Mean (SD)	64.6 (12.02)
	Median	67
	Min, Max	(38, 79)
Age group, n (%)	18-64	5 (33.3)
	65-74	7 (46.7)
	≥75	3 (20.0)
Sex, n (%)	Male	5 (33.3)
	Female	10 (66.7)
Ethnicity, n (%)	Hispanic or Latino	6 (40.0)
	Not Hispanic or Latino	9 (60.0)
Race, n (%)	Black or African American	1 (6.7)
	White	13 (86.7)
	Other	1 (6.7)
Region, n (%)	USA	15 (100.0)
Height (cm)	n	13
	Mean (SD)	167.88 (13.351)
	Median	162.56
	Min, Max	(147.3, 188.0)
Weight (kg)	n	15
	Mean (SD)	84.70 (22.255)
	Median	78.02
	Min, Max	(58.1, 135.2)
BMI (kg/m^2)	n	13
	Mean (SD)	30.30 (7.381)
	Median	27.72
	Min, Max	(21.6, 45.3)
Hemoglobin (g/dL)	n	15
	Mean (SD)	10.05 (0.931)
	Median	10.3
	Min, Max	(8.3, 11.2)
Hemoglobin Group, n (%)	≤10 g/dL	6 (40.0)
	>10 g/dL	9 (60.0)
Ferritin (ng/mL)	n	15
	Mean (SD)	246.7 (211.86)
	Median	138
	Min, Max	(31, 727)
Ferritin Group, n (%)	≤100 ng/mL	5 (33.3)
	>100 ng/mL	10 (66.7)
TSAT (%)	n	15
	Mean (SD)	25.9 (16.50)
	Median	20
	Min, Max	(12, 78)
TSAT Group, n (%)	≤20%	8 (53.3)
	>20%	7 (46.7)
Iron Repletion Status	Ferritin≥100 ng/mL and TSAT ≥20%	7 (46.7)
	Ferritin<100 ng/mL or TSAT<20%	8 (53.3)

Notes: Age is calculated in Years from subject's birth date to date of informed consent; Hb baseline is defined as the mean of the central laboratory Hb value from the baseline visit at Day 1 (prior to receiving the first dose of study drug in this study), plus any other central lab Hb values within 15 days prior to Day 1; Baseline of other assessments is defined as the last available value obtained prior to the first dose of study drug in this study.

Results

Roxadustat Treatment

- The mean and median duration of exposure was 157.5 and 137.7 weeks, respectively.
- The maximum patient exposure was 335 weeks or 6.4 years.

Table 2. Duration of Roxadustat Treatment

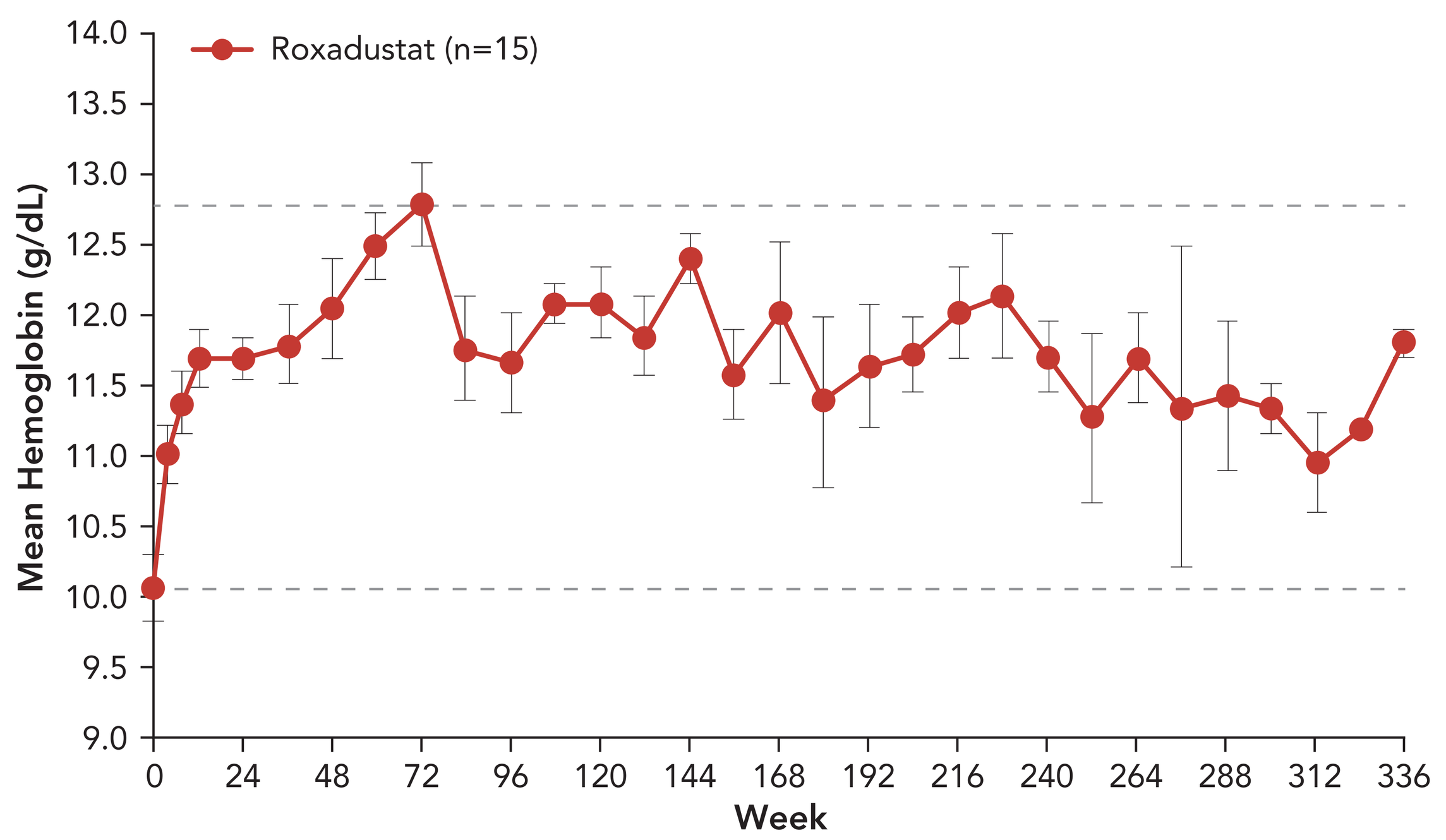
Statistics/Category	Roxadustat (N=15)
Duration (week)	
n	15
Mean (SD)	157.5 (114.35)
Median	137.7
Min, Max	(<2, 335)
Average (Patient Exposure Year)	3
Sum (Patient Exposure Year)	45.3
<2 weeks	1 (6.7)
2 - <26 weeks	0
26 - <52 weeks	2 (13.3)
52 - <76 weeks	2 (13.3)
76 - <104 weeks	2 (13.3)
104 - <156 weeks	2 (13.3)
156 - <208weeks	1 (6.7)
208 - <260 weeks	1 (6.7)
260 - <312 weeks	2 (13.3)
≥312 weeks	2 (13.3)

Note: Duration in week = (the date of last dose taken - the date of first dose taken +1)/7.

Change in Hemoglobin Over Time

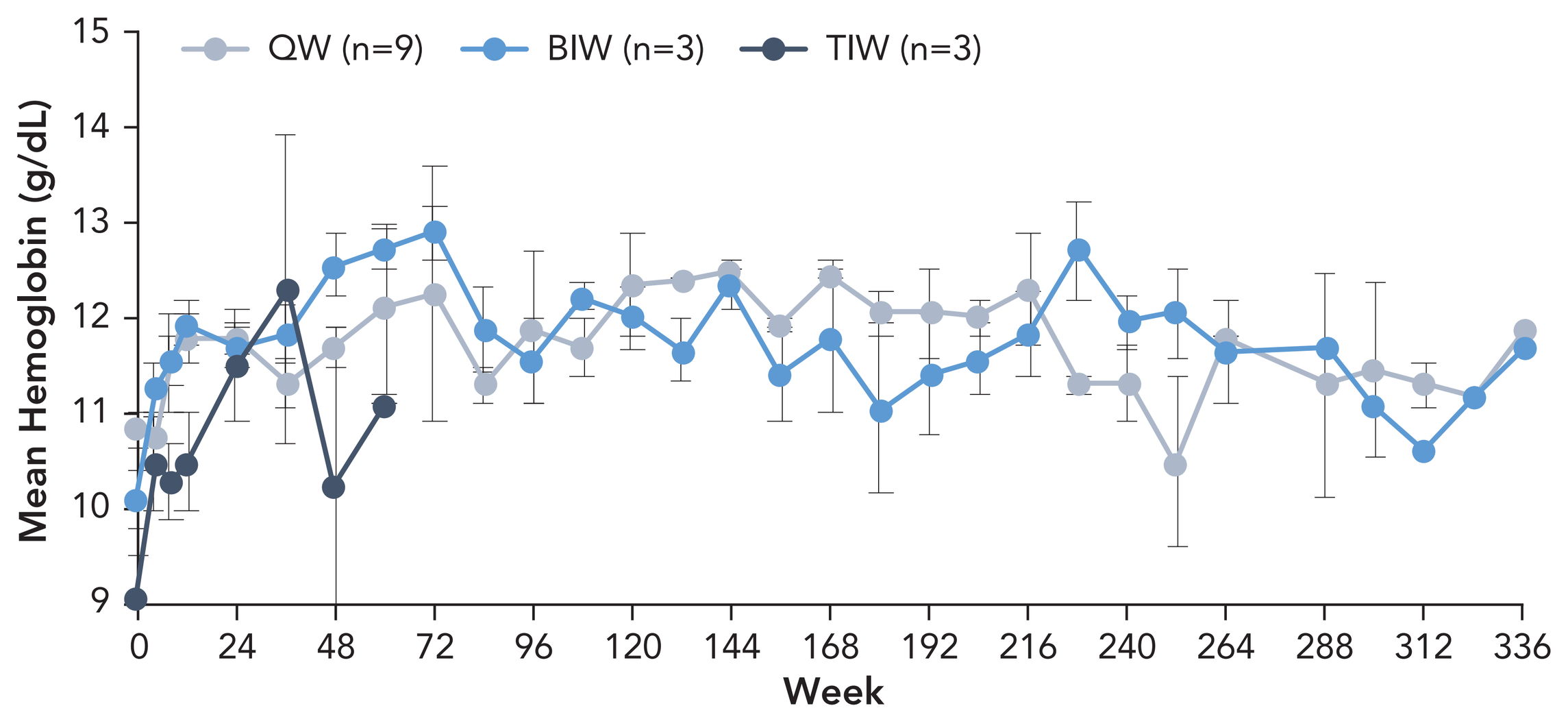
- There was a gradual increase in mean Hb values starting as early as Week 4, and after Week 12 Hb values were maintained through the end of study in patients overall and among subgroups based on dosing frequency.
- Hb levels over time averaged 11.7 g/dL [range, 9.1-12.9 g/dL]. The mean time (days) elapsed between the last roxadustat dose in the parent protocol and first dose in this protocol was 112.0 days (min: 8 days, max: 178 days).

Figure 1. Mean (+/- SE) Hemoglobin (g/dL) from Baseline Over Time (Overall)



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

Figure 2. Mean (+/- SE) Hemoglobin (g/dL) from Baseline Over Time by Dose Frequency

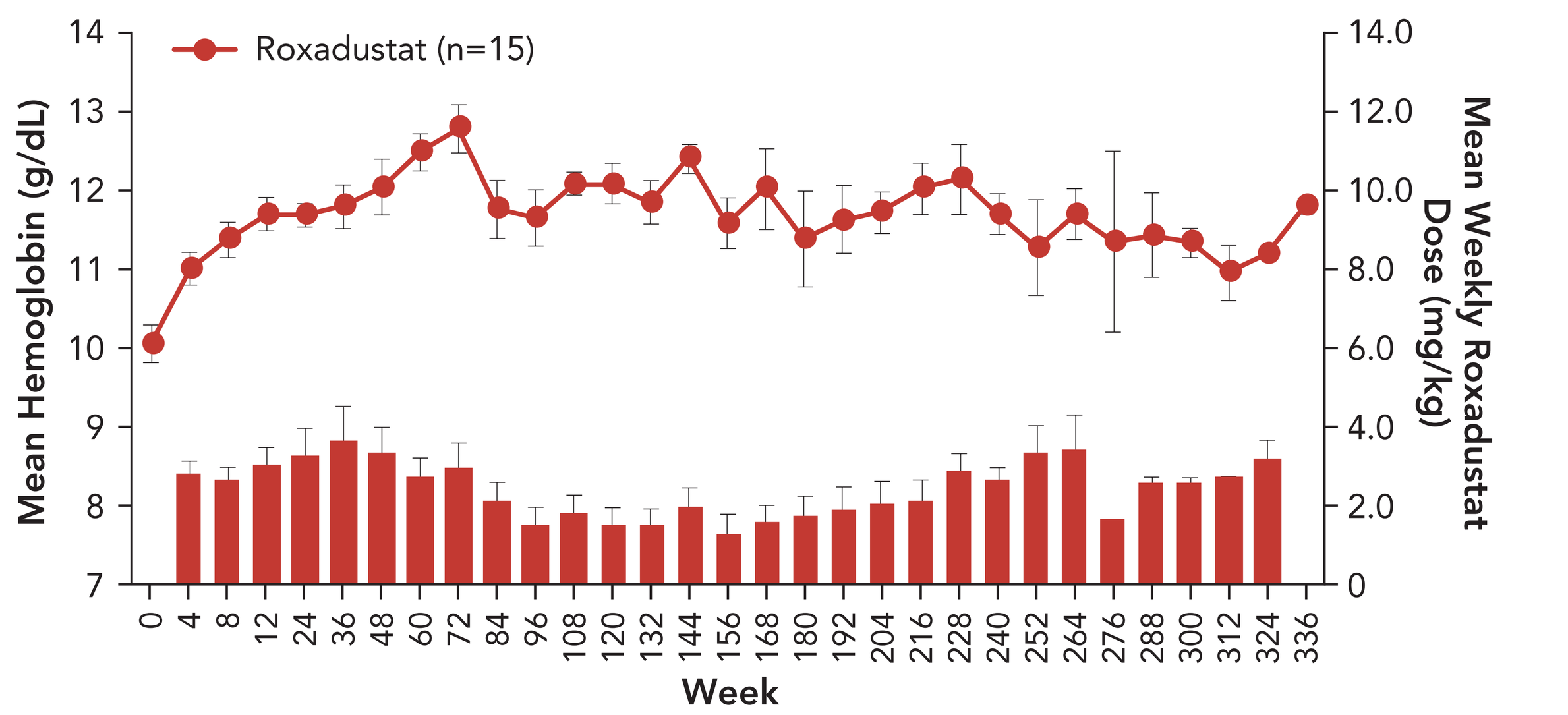


Note: n is the number of subjects with non-missing value at each week.

Roxadustat Dosing Frequency Over Time

- At the time of enrollment, 3/15 of subjects were on TIW dosing regimen, 9/15 on BIW, and 3/15 on QW.
- At patients' last dose, 3/15 of subjects were on TIW dosing regimen, 10/15 on BIW, and 2/15 were on QW dosing regimens.

Figure 3. Mean (+/- SE) Hemoglobin (g/dL) from Baseline Over Time All Subjects

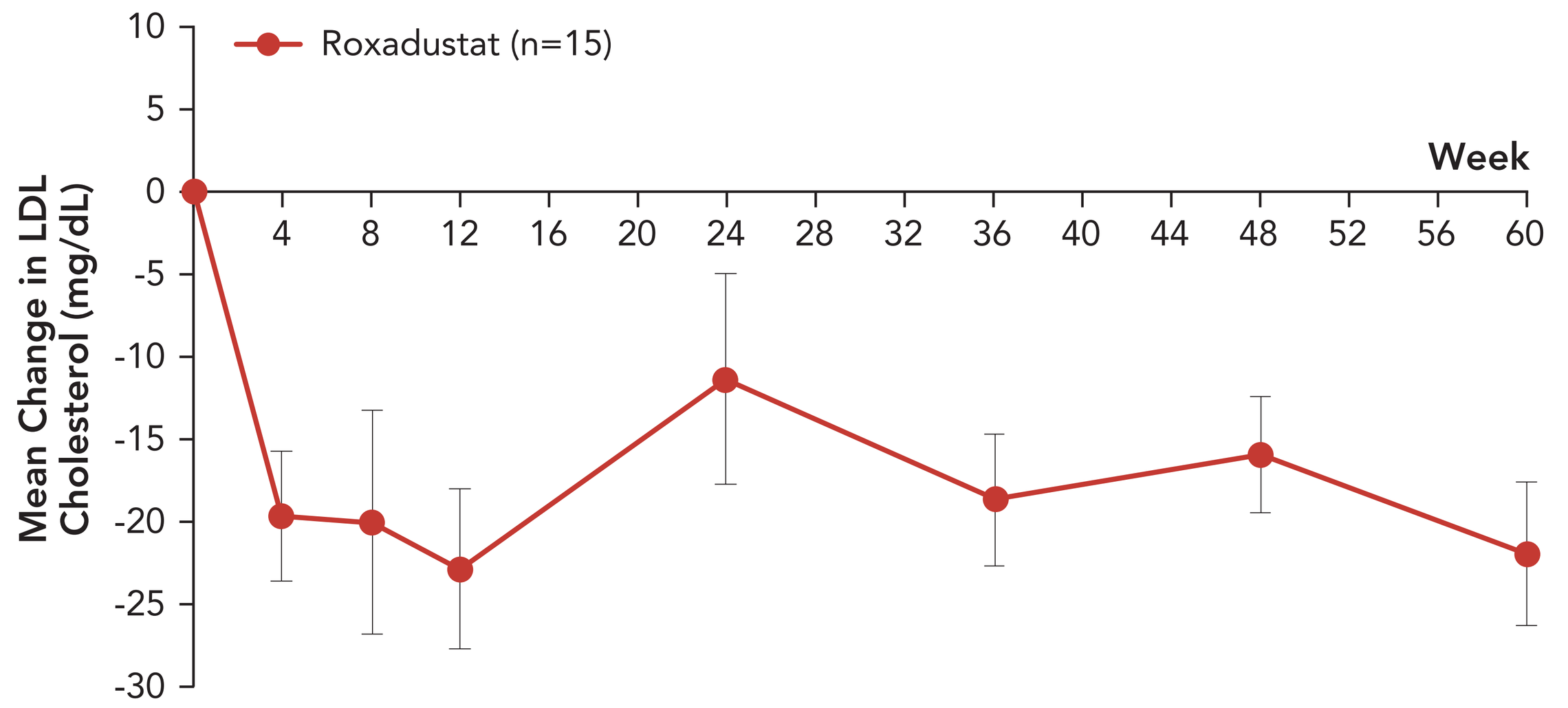


Note: n is the number of subjects with non-missing value at each week.

LDL Over Time

- Consistent with the Phase 2 and 3 studies, roxadustat decreased mean LDL cholesterol levels within the first 4 weeks of treatment (from a baseline of 88.8 mg/dL).

Figure 3. Mean Change in LDL Cholesterol (mg/dL)



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

Safety

- The most common AE was upper respiratory tract infection that was seen in 40% (n=6; events*100/PEY=19.9) of the patients; followed by cough in 33.3% (n=5; events*100/PEY=13.2), abdominal pain (events*100/PEY=6.6), bronchitis (events*100/PEY=6.6), urinary tract infection (events*100/PEY=6.6), and hypoglycemia (events*100/PEY=8.8) in 20.0% (n=3) each.
- There were two deaths during the study.
  - One patient died on Day 973 of the study, 9 days after the last dose of roxadustat. The patient was a 76 year-old woman with a history COPD, CHF, morbid obesity, HTN, and DM. She experienced an event of CHF and respiratory arrest at home, requiring emergency CPR and intubation/mechanical ventilation. She was found to have post-arrest hypoxia-induced encephalopathy and was made DNR, was extubated, and died from respiratory failure. Her death was considered not related to roxadusat per PI.
  - The second patient died on Day 1452 of the study, 10 days after his last dose of roxadustat. He was a 68 year-old man with a history of coronary artery disease, atrial fibrillation, bronchiolitis obliterans with organizing pneumonia, and diabetes mellitus type 2. He became acutely unresponsive at home, requiring CPR and intubation. He also developed anoxic encephalopathy while hospitalized, was made DNR, and died.

Table 3. Adverse Event Summary by Preferred Term

System Organ Class Preferred Term	Roxadustat N=15 n (%)	PEY=45.3 Events (Events*100/PEY)
Any Treatment-Emergent Serious Adverse Events (TESAE)	9 (60.0)	30 (66.2)
Blood and Lymphatic System Disorders	1 (6.7)	1 (2.2)
Haemorrhagic Anaemia	1 (6.7)	1 (2.2)
Cardiac Disorders	4 (26.7)	10 (22.1)
Acute Coronary Syndrome	1 (6.7)	1 (2.2)
Acute Myocardial Infarction	2 (13.3)	3 (6.6)
Angina Pectoris	1 (6.7)	1 (2.2)
Angina Unstable	1 (6.7)	1 (2.2)
Atrial Fibrillation	1 (6.7)	1 (2.2)
Cardiac Failure	1 (6.7)	1 (2.2)
Cardiac Failure Congestive	1 (6.7)	1 (2.2)
Ventricular Fibrillation	1 (6.7)	1 (2.2)
Gastrointestinal Disorders	1 (6.7)	1 (2.2)
Epiploic Appendagitis	1 (6.7)	1 (2.2)
General Disorders and Administration Site Conditions	1 (6.7)	1 (2.2)
Gait Disturbance	1 (6.7)	1 (2.2)
Infections and Infestations	4 (26.7)	8 (17.7)
Cellulitis	1 (6.7)	3 (6.6)
Clostridium Difficile Colitis	1 (6.7)	1 (2.2)
Pneumonia	2 (13.3)	2 (4.4)
Sepsis	1 (6.7)	1 (2.2)
Urinary Tract Infection	1 (6.7)	1 (2.2)
Injury, Poisoning and Procedural Complications	1 (6.7)	2 (4.4)
Fall	1 (6.7)	1 (2.2)
Humerus Fracture	1 (6.7)	1 (2.2)
Nervous System Disorders	1 (6.7)	1 (2.2)
Hypoxic-Ischaemic Encephalopathy	1 (6.7)	1 (2.2)
Renal Andurinary Disorders	3 (20.0)	3 (6.6)
Chronic Kidney Disease	2 (13.3)	2 (4.4)
Renal Tubular Necrosis	1 (6.7)	1 (2.2)
Respiratory, Thoracic and Mediastinal Disorders	2 (13.3)	3 (6.6)
Acute Respiratory Failure	1 (6.7)	2 (4.4)
Respiratory Failure	1 (6.7)	1 (2.2)

Notes: An AE (classified by preferred term) occurring after the first dose of study medication and up to the last dose of study medication is considered a treatment emergent adverse event (TEAE) if it was not present prior to the first dose of study medication, or it was present prior to the first dose of study medication but increased in severity during the treatment period; Subjects with more than one event in a category were counted only once for that category; Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary version 15.1.

Conclusions

- In this cohort of patients, long-term use of roxadustat for treatment of anemia resulted in continued efficacy in Hb maintenance in all patients.
- The safety profile was consistent with the population of patients under study.