Roxadustat for the Maintenance Treatment of Anemia in End-Stage Kidney Disease Patients on Stable Dialysis: A Phase 3, Randomized, Open-Label, Active-Controlled Study (PYRENEES)

Running Head: Roxadustat to Treat Anemia in Dialysis Patients

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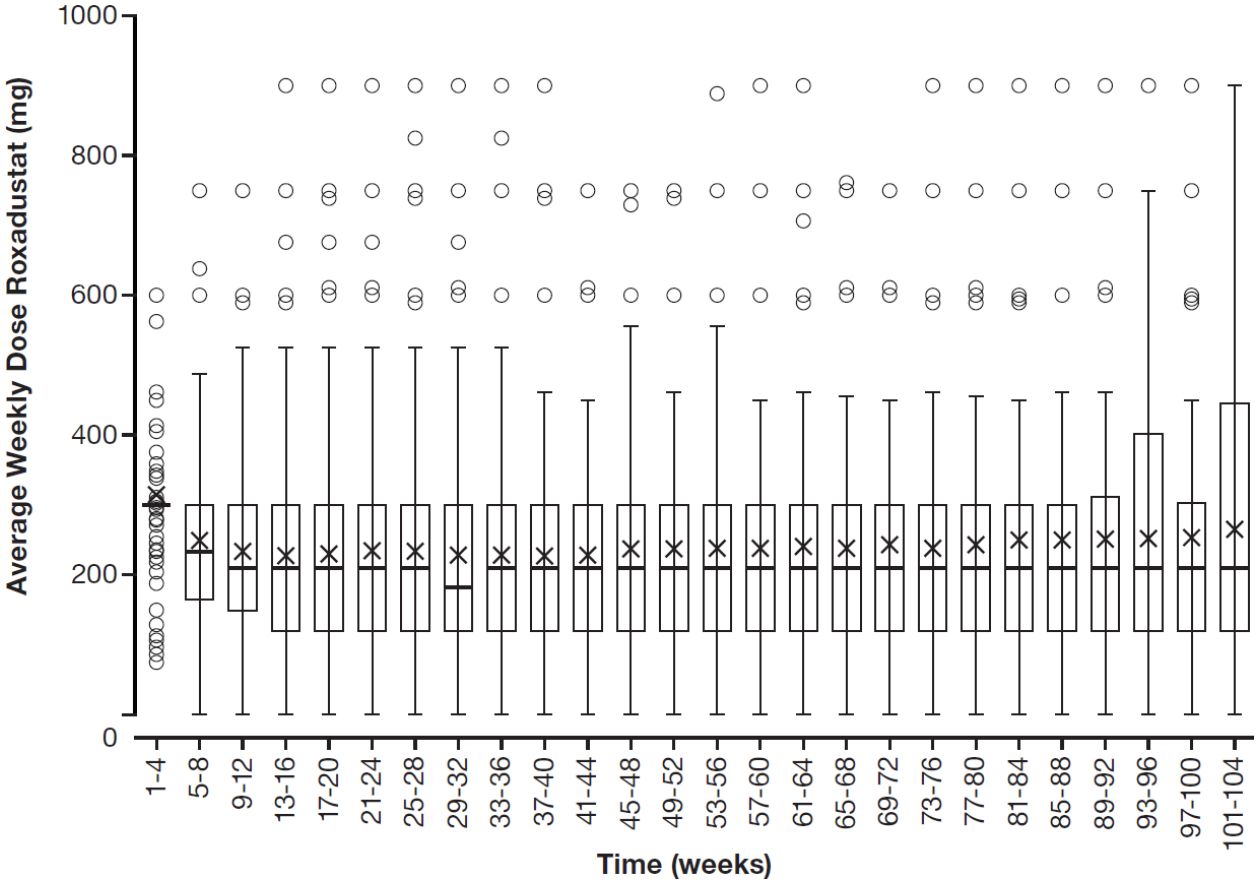
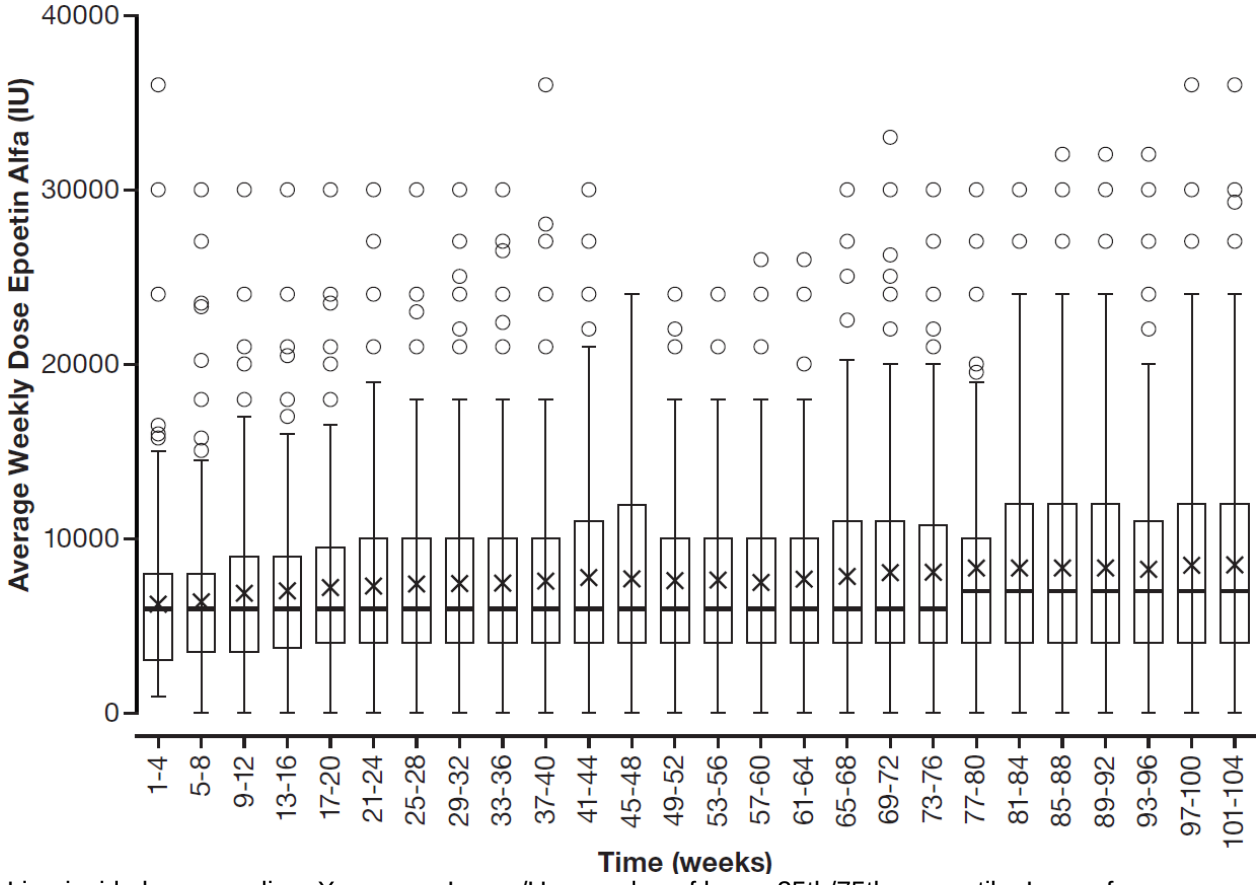
Supplemental Figure S1. Average Weekly Dose of Roxadustat (Safety Analysis Set)



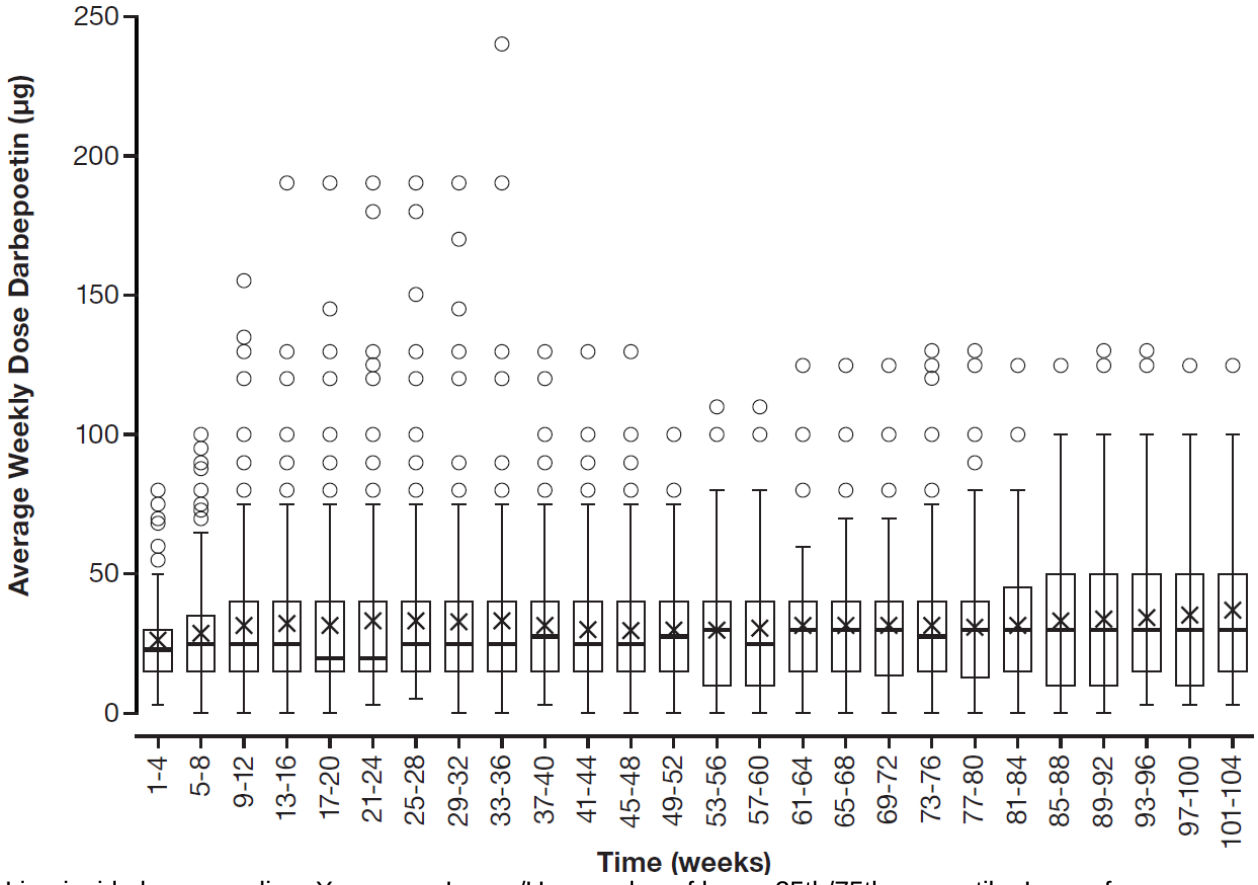
Line inside box = median, X = mean, Lower/Upper edge of box = 25th/75th percentile, Lower fence = 1.5 x interquartile range below 25th percentile, Upper fence = 1.5 x interquartile range above 75th percentile.

Supplemental Figure S2. Average Weekly Dose of Epoetin Alfa (Safety Analysis Set)



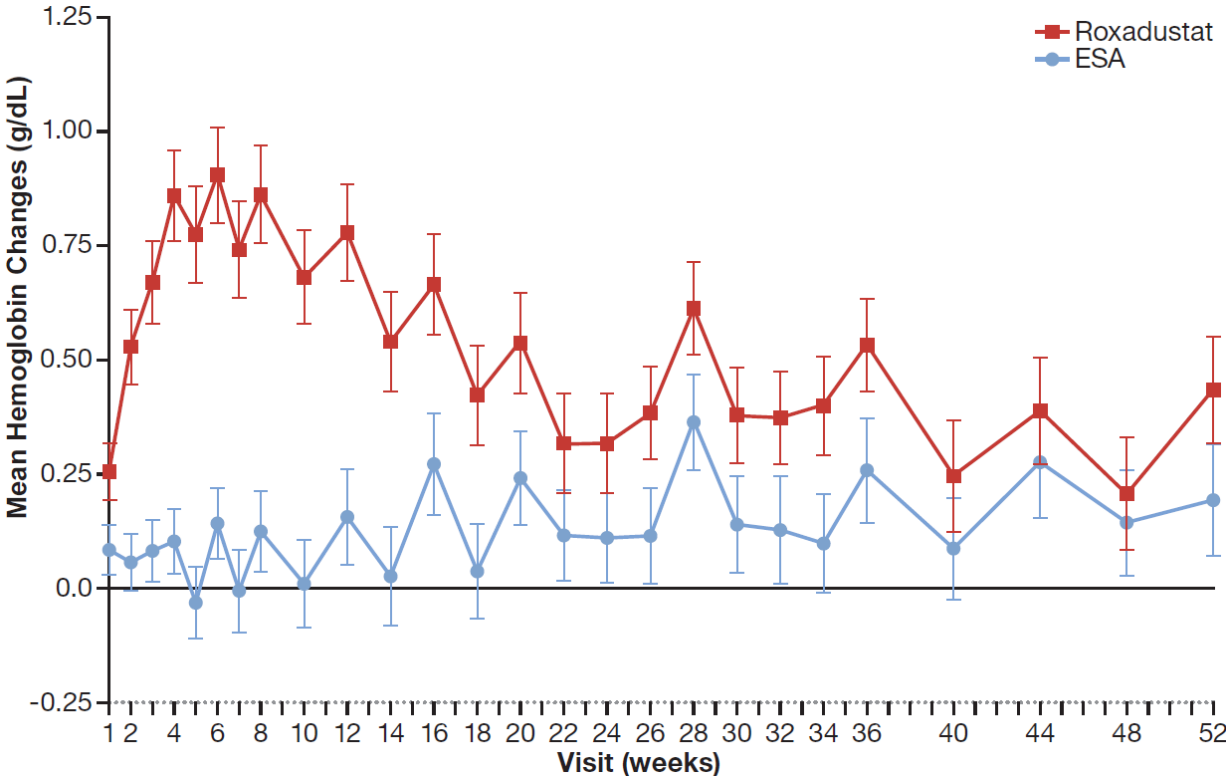
Line inside box = median, X = mean, Lower/Upper edge of box = 25th/75th percentile, Lower fence = 1.5 x interquartile range below 25th percentile, Upper fence = 1.5 x interquartile range above 75th percentile.

Supplemental Figure S3. Average Weekly Dose of Darbepoetin Alfa (Safety Analysis Set)



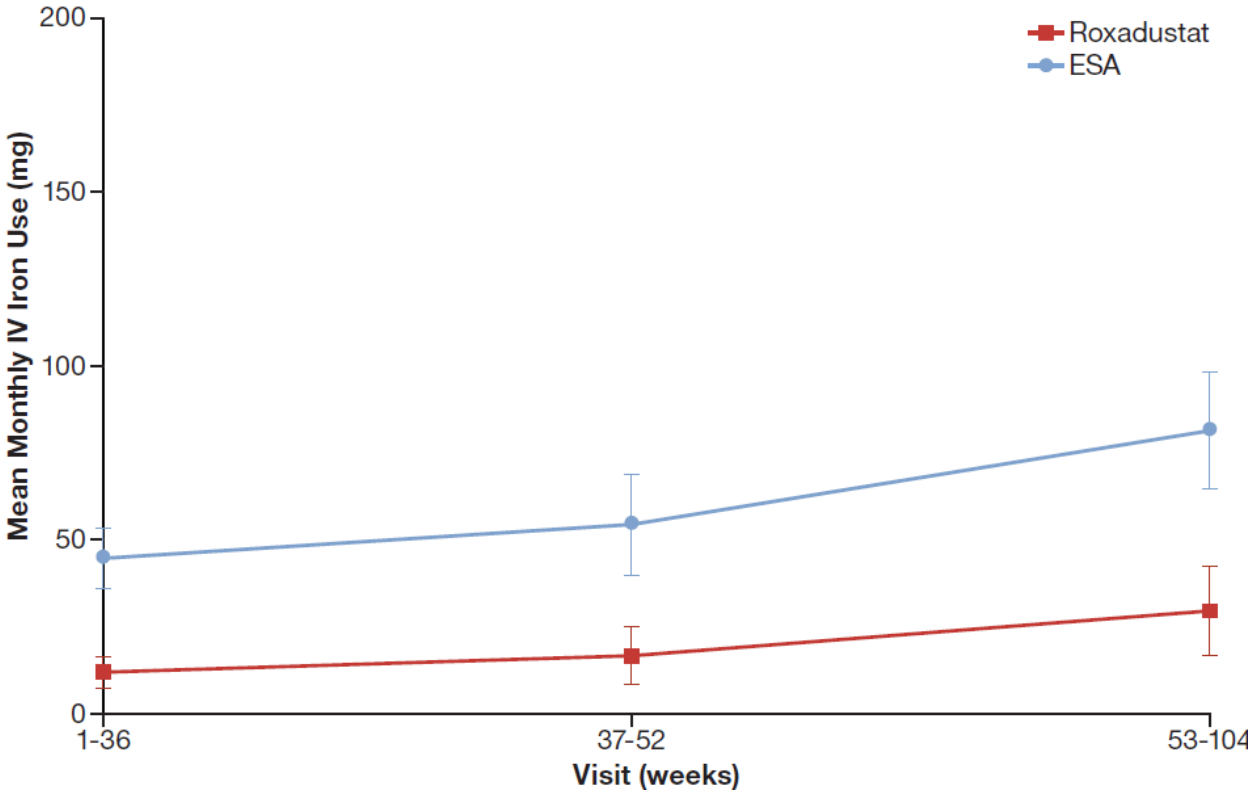
Line inside box = median, X = mean, Lower/Upper edge of box = 25th/75th percentile, Lower fence = 1.5 x interquartile range below 25th percentile, Upper fence = 1.5 x interquartile range above 75th percentile.

Supplemental Figure S4. Mean (±95% CI) Hb Change From Baseline to Week 52 (Per Protocol Set)



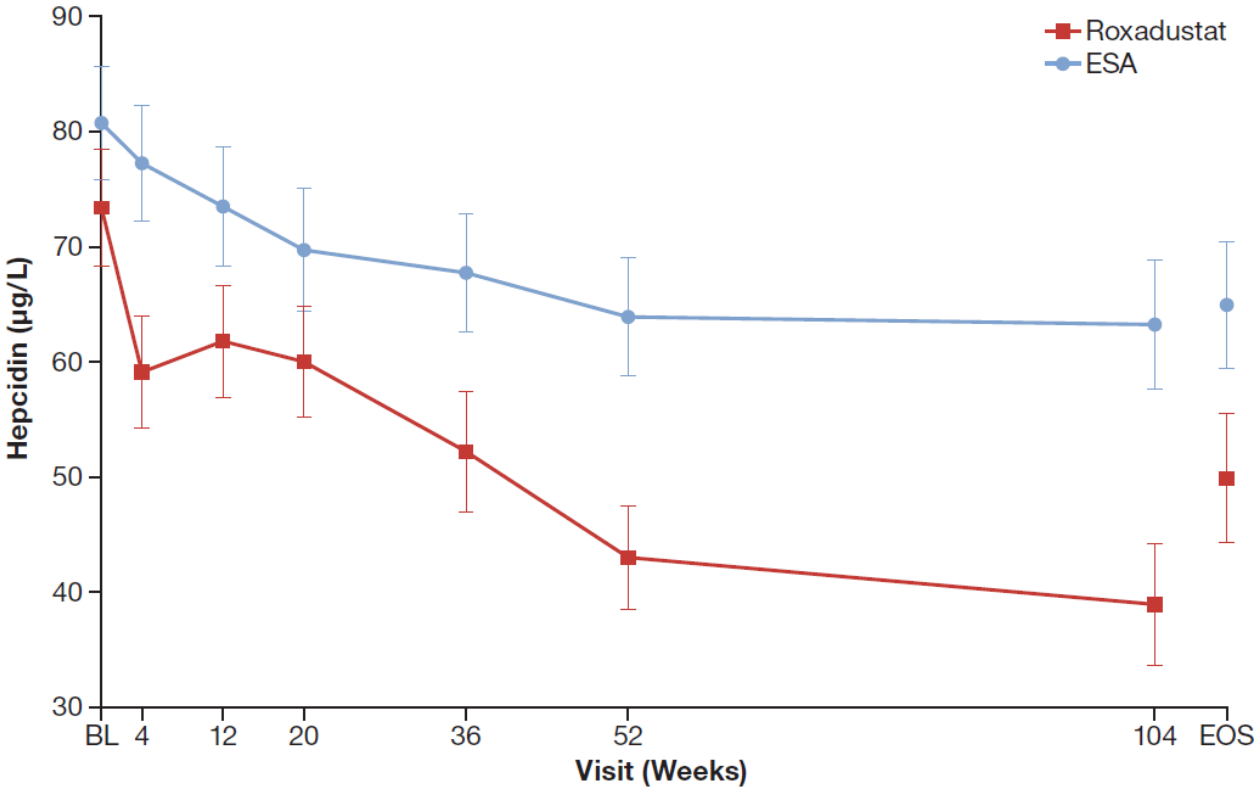
Abbreviations: CI, confidence interval; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin.

Supplemental Figure S5. Mean (±95% CI) Monthly Use of IV Iron (Full Analysis Set)



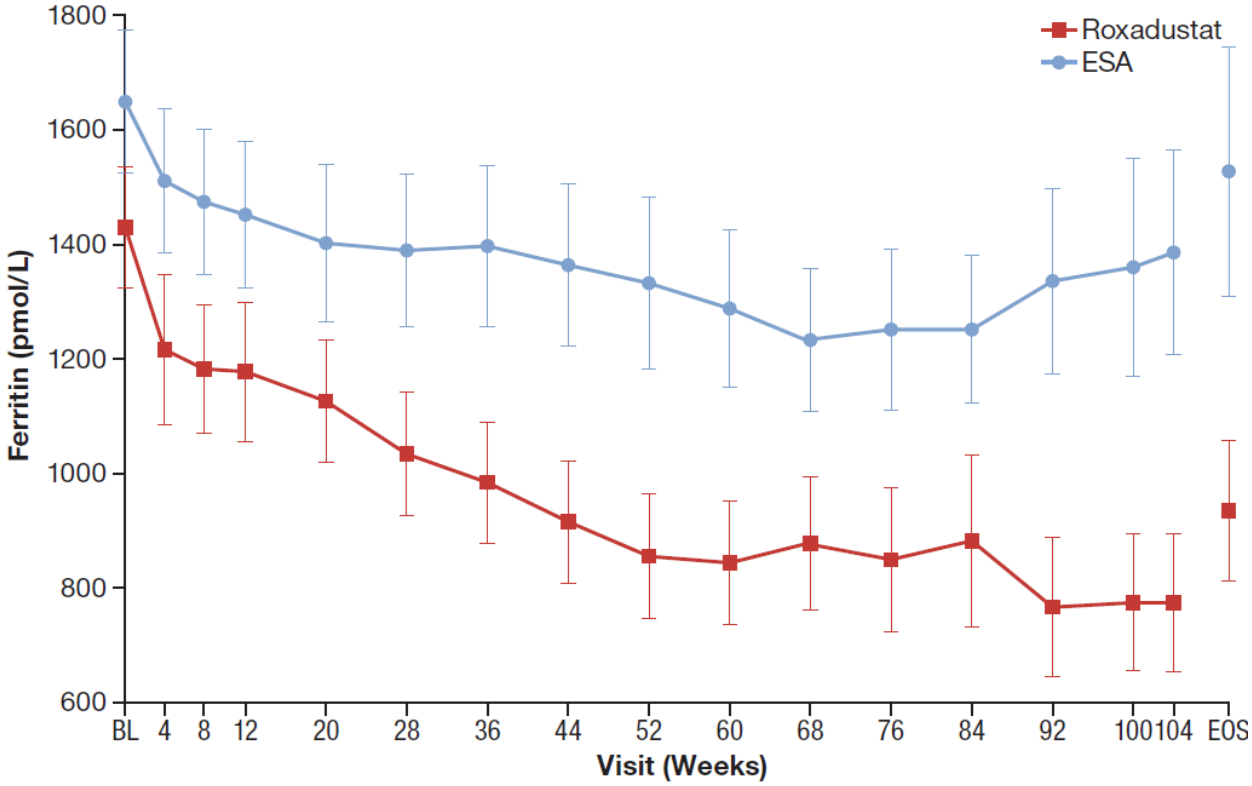
Abbreviations: CI, confidence interval; ESA, erythropoiesis-stimulating agent; IV, intravenous.

Supplemental Figure S6. Mean (±95% CI) Hepcidin Levels by Visit (Full Analysis Set)



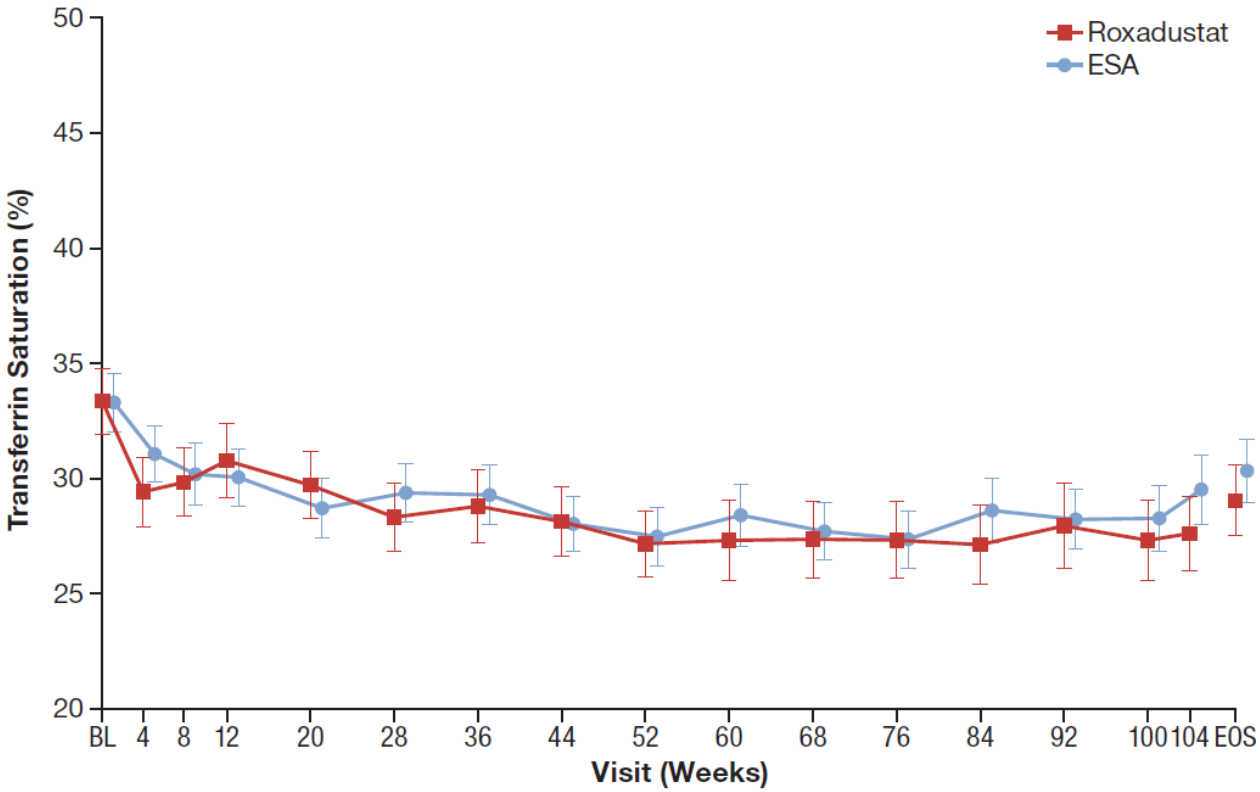
Abbreviations: BL, baseline; CI, confidence interval; EOS, end of study; ESA, erythropoiesis-stimulating agent.

Supplemental Figure S7. Mean (±95% CI) Ferritin Levels by Visit (Full Analysis Set)



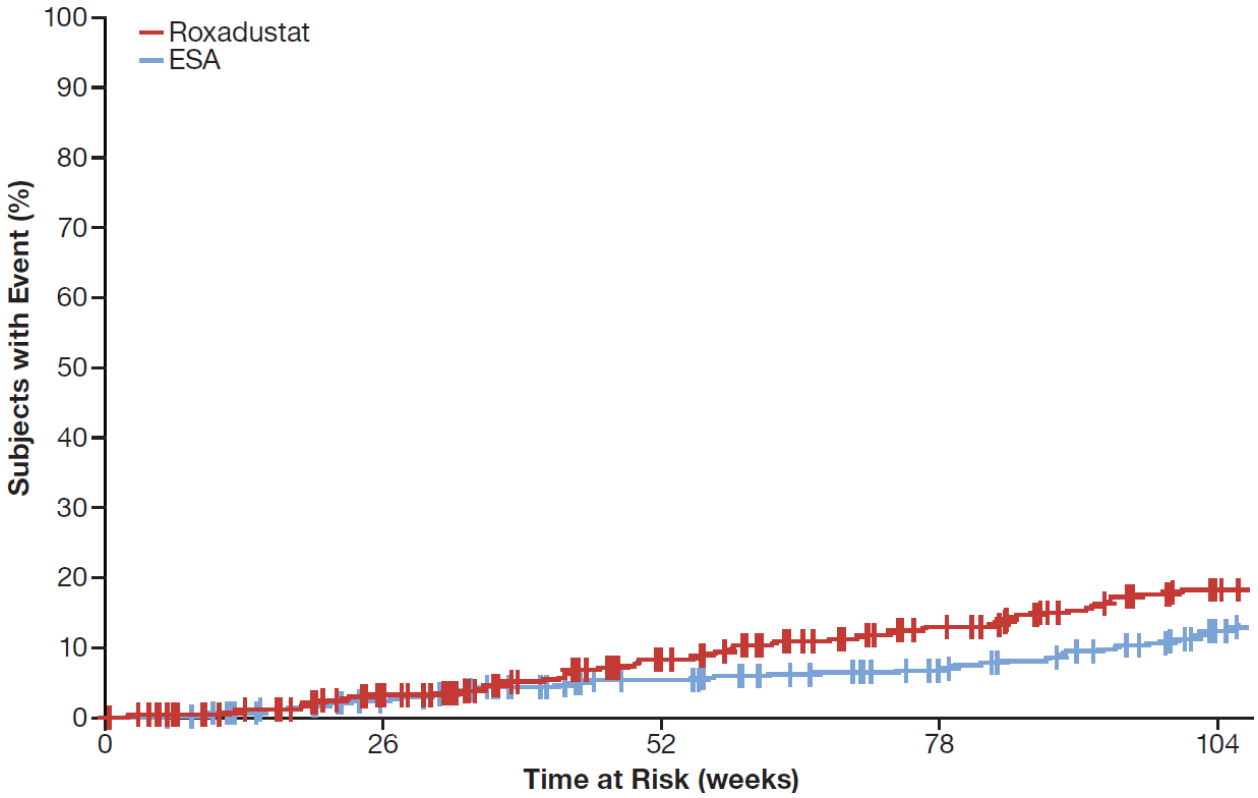
Abbreviations: BL, baseline; CI, confidence interval; EOS, end of study; ESA, erythropoiesis-stimulating agent.

Supplemental Figure S8. Mean (±95% CI) Transferrin Saturation Levels by Visit (Full Analysis Set)



Abbreviations: BL, baseline; CI, confidence interval; EOS, end of study; ESA, erythropoiesis-stimulating agent.

Supplemental Figure S9. Cumulative Incidence of Deaths Occurring During the Safety Emergent Period (Safety Analysis Set)



Abbreviation: ESA, erythropoiesis-stimulating agent.

Supplemental Table S1. Dose Conversion Between Average Doses of Epoetin and Darbepoetin Alfa Before Study Registration and Roxadustat

Epoetin[a] (IU/week)	Darbepoetin Alfa[a] (μg/week)	Roxadustat (mg/dose)
<8000	<40	100
8000-16000	40-80	150[b]
>16000	>80	200[c]

[a]Average dose prescribed weekly in the last 4 weeks prior to randomization.
[b]If the initial dose of 150 mg exceeded the maximum dose of 3.0 mg/kg, then 100 mg was to be used as the starting dose.
[c]If the initial dose of 200 mg exceeded the maximum dose of 3.0 mg/kg, then 150 mg was to be used as the starting dose.
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Supplemental Table S2. Dose-Adjusting Criteria for Roxadustat

Change in Hb over the previous 4 weeks (g/dL)	Current Hb Level (g/dL)		
	<10.5	≥10.5 to <12.0	≥12.0 to <13.0
< –1	One-step increase	One-step increase	No change
≥ –1 to ≤1	One-step increase	No change	One-step reduction
> 1	No change	One-step reduction	One-step reduction

Abbreviation: Hb, hemoglobin.

Supplemental Table S3. Dose Adjustment Steps

Step	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Dose (mg)	20	40	50	70	100	150	200	250	300	400

Supplemental Table S4. Criteria for Excluding a Patient From Per Protocol Set

1	Subject who receives <12 weeks of study treatment.
2	Subject without a valid corresponding Hb. A valid corresponding Hb is defined as an Hb value from the central laboratory that is measured at least 2 weeks after the first dose and was either before the last study drug intake or at maximum three days after the last drug intake.
3	Prescribed study drug compliance during treatment < 75% during the first 36 weeks analysis period.
4	Violation of inclusion or exclusion criteria which may affect the assessment of the efficacy of the study drug.
5	Administration of wrong randomization study drug for more than one week during the reference period (first 36 weeks) or until EOT, whatever comes first.
6	Administration of prohibited concomitant medication affecting efficacy during the reference period (first 36 weeks) or until EOT, whatever comes first.
7	Administration of rescue therapy significantly deviating from the protocol during the reference period (first 36 weeks) or until EOT, whatever comes first.

Abbreviations: EOT, end of treatment; Hb, hemoglobin.

Supplemental Table S5. Schedule of Assessments

Visit/Week	Screening (2-6 weeks)			Treatment Period					Follow-up	
	S1	**S2**	**S3**	**D1**	**Weekly**	**Every 2 weeks**	**Every 4 weeks**	**EoT**	**EoT +2 weeks**	**EoS (EoT + 4 weeks)**
					1-8	**10-36**	**40-100**	**104**		
Serum lipid panel	x			x	w4, 8	w12, 20, 28, 36	w44, 52, 68, 84	x		x
Body weight	x	x	x	x		w12, 24, 36	w52, 76	x		x
Blood pressure	x	x	x	x	x	x	x	x		x
Hemoglobin		x	x		x	x	x		x	
QoL questionnaires				x	w8	w12, 28, 36	w52, 76		x	
hs-CRP and hepcidin				x	w4	w12, 20, 36	w52	x		x
Adverse events	←									→

Abbreviations: D, day; EoS, end of study; EoT, end of treatment; hs-CRP, high-sensitivity C-reactive protein; QoL, quality of life; w, week.

Supplemental Table S6. Demographics and Baseline Characteristics by Subgroup (Safety Analysis Set)

Parameter	Subgroup: Darbepoetin		Subgroup: Epoetin	
	Roxadustat	Darbepoetin Alfa	Roxadustat	Epoetin Alfa
	(n=158)	(n=163)	(n=256)	(n=257)
Sex, male, n (%)	97 (61.4)	98 (60.1)	148 (57.8)	137 (53.3)
Race, white, n (%)	153 (96.8)	156 (95.7)	252 (98.4)	251 (97.7)
Age, years, mean (SD)	61.1 (14.3)	61.8 (12.6)	61.0 (13.6)	61.9 (14.0)
Weight, kg, mean (SD)	76.27 (15.75)	76.70 (16.65)	76.30 (15.99)	75.84 (17.65)
BMI, kg/m^2, mean (SD)	26.70 (4.81)	26.81 (5.30)	26.97 (4.89)	27.05 (5.78)
Hb, g/dL, mean (SD)	10.70 (0.60)	10.74 (0.64)	10.78 (0.63)	10.80 (0.61)
LDL cholesterol, mmol/L, n (%)				
≤ ULN	86 (54.4)	92 (56.4)	123 (48.0)	140 (54.5)
> ULN	72 (45.6)	71 (43.6)	133 (52.0)	117 (45.5)
Previous ESA dose/week, n (%)				
<25 µg darbepoetin alfa or <5000 IU epoetin	96 (60.8)	86 (52.8)	126 (49.2)	103 (40.1)
25 to <40 µg darbepoetin or 5000 to <8000 IU epoetin	40 (25.3)	56 (34.4)	71 (27.7)	77 (30.0)
40 to <80 µg darbepoetin or 8000 to <16000 IU epoetin	20 (12.7)	21 (12.9)	57 (22.3)	72 (28.0)
≥80 µg darbepoetin or ≥16000 IU epoetin	2 (1.3)	0	2 (0.8)	5 (1.9)
Baseline dialysis type, n (%)				
Hemodialysis	134 (84.8)	150 (92.0)	245 (95.7)	255 (99.2)
Peritoneal dialysis	24 (15.2)	13 (8.0)	11 (4.3)	2 (0.8)
Baseline hs-CRP, nmol/L, n (%)				
≤ ULN	83 (52.5)	87 (53.4)	127 (49.6)	139 (54.1)
> ULN	75 (47.5)	76 (46.6)	129 (50.4)	118 (45.9)
Dialysis vintage, years				
Mean (SD)	3.89 (3.65)	4.76 (4.23)	4.63 (4.46)	3.67 (3.17)
Median (min, max)	2.75 (0.38, 20.88)	3.41 (0.33, 20.86)	3.14 (0.35, 27.04)	2.60 (0.34, 17.36)
Iron repletion at baseline, n (%)				
Ferritin ≥100 ng/mL and TSAT ≥20%	135 (85.4)	144 (88.3)	220 (86.3)	222 (86.4)
Blood pressure, mmHg, mean (SD)				
Systolic	134.6 (16.9)	136.7 (19.3)	135.5 (18.0)	137.0 (18.7)
Diastolic	75.5 (10.6)	74.6 (11.3)	75.1 (11.3)	74.1 (11.2)
History of cardiovascular, cerebrovascular, or thromboembolic diseases, n (%)	55 (34.8)	70 (42.9)	114 (44.5)	131 (51.0)
History of diabetes, n (%)	43 (27.2)	52 (31.9)	61 (23.8)	81 (31.5)

Abbreviations: BMI, body mass index; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; hs-CRP, high-sensitivity C-reactive protein; IU, international unit; LDL, low-density lipoprotein; SD, standard deviation; TSAT, transferrin saturation; ULN, upper limit of normal.

Supplemental Table S7. Subgroup Analysis of Change in Hb Levels From Baseline to the Average of Weeks 28-36 (Per Protocol Set)

	Darbepoetin Subgroup		Epoetin Subgroup	
	Roxadustat (n=147)	**Darbepoetin (n=153)**	**Roxadustat (n=239)**	**Epoetin (n=244)**
Baseline Hb, g/dL	10.680 (0.595)	10.729 (0.643)	10.799 (0.635)	10.798 (0.619)
Average Hb (Weeks 28-36), g/dL n	11.189 (0.608) 137	11.017 (0.771) 148	11.257 (0.701) 217	10.955 (0.782) 233
Hb change from BL to average of Weeks 28-36 n	0.512 (0.752) 137	0.286 (0.998) 148	0.455 (0.849) 217	0.153 (0.901) 233
LSM (95% CI) change from BL to average of Weeks 28-36	0.493 (0.370, 0.616)	0.318 (0.199, 0.436)	0.409 (0.308, 0.509)	0.140 (0.043, 0.238)
LSM difference (roxadustat – ESA) (95% CI)	0.175 (0.013, 0.337)		0.268 (0.134, 0.403)	

Data are reported as mean (SD) unless otherwise indicated.
Abbreviations: BL, baseline; CI, confidence interval; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; LSM, least squares mean; SD, standard deviation.

Supplemental Table S8. Subgroup Analysis of Change in Hb Levels From Baseline to the Average of Weeks 28-52 (All Randomized Patients)

	Darbepoetin Subgroup		Epoetin Subgroup	
	Roxadustat (n=158)	**Darbepoetin (n=163)**	**Roxadustat (n=257)**	**Epoetin (n=258)**
Baseline Hb, g/dL n	10.701 (0.595) 158	10.737 (0.638) 163	10.776 (0.630) 256	10.799 (0.609) 257
Average Hb (Weeks 28-52), g/dL n	11.136 (0.528) 139	11.027 (0.652) 153	11.150 (0.664) 225	10.917 (0.664) 240
Hb change from BL to average of Weeks 28-52 n	0.454 (0.683) 139	0.291 (0.850) 153	0.361 (0.823) 225	0.114 (0.862) 240
LSM (95% CI) change from BL to average of Weeks 28-52	0.504 (0.392, 0.617)	0.349 (0.244, 0.455)	0.265 (0.168, 0.362)	0.081 (-0.010, 0.172)
LSM difference (roxadustat – ESA) (95% CI)	0.155 (0.021, 0.290)		0.184 (0.066, 0.301)	

Data are reported as mean (SD) unless otherwise indicated.
Abbreviations: BL, baseline; CI, confidence interval; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; LSM, least squares mean; SD, standard deviation.

Supplemental Table S9. Treatment-Emergent Adverse Events Leading to Death (≥0.5% Patients in Any Treatment Group; Safety Analysis Set)

MedDRA v20.0 Preferred Term	Roxadustat (n=414)	ESA (n=420)
Sudden death	7 (1.7)	3 (0.7)
Acute myocardial infarction	4 (1.0)	6 (1.4)
Death	6 (1.4)	3 (0.7)
Pneumonia	2 (0.5)	6 (1.4)
Cardiac arrest	2 (0.5)	6 (1.4)
Cardiac failure	5 (1.2)	3 (0.7)
Sepsis	4 (1.0)	3 (0.7)
Acute coronary syndrome	3 (0.7)	1 (0.2)
Cardiopulmonary failure	3 (0.7)	1 (0.2)
Cardiac failure acute	3 (0.7)	0
Intestinal ischaemia	1 (0.2)	2 (0.5)
Myocardial infarction	0	2 (0.5)

Data are reported as n (%).
The safety analysis set included all randomized patients who received ≥1 dose of study drug.
Abbreviation: ESA, erythropoiesis-stimulating agent.

Supplemental Table S10. Proportional Hazards Regression of Deaths During the Safety Emergent Period by Covariate (Safety Analysis Set)

	All		Subgroup DA		Subgroup Epoetin	
Categorical Covariate	**Hazard Ratio[a] (95% CI)**	***P*-value**	**Hazard Ratio[a] (95% CI)**	***P*-value**	**Hazard Ratio[a] (95% CI)**	***P*-value**
Age ≥65 vs <65 (years)	1.549 (1.068, 2.246)	0.021	0.981 (0.497, 1.936)	0.956	1.902 (1.208, 2.995)	0.005
Age ≥75 vs <75 (years)	1.594 (1.099, 2.313)	0.014	1.007 (0.509, 1.994)	0.984	1.944 (1.235, 3.058)	0.004
Prior ESA type (epoetin vs DA)	1.596 (1.101, 2.312)	0.014	-	-	-	-
Prior ESA dose: Low vs high[b]	1.745 (1.195, 2.548)	0.004	1.110 (0.557, 2.212)	0.767	2.151 (1.353, 3.418)	0.001
History of cardiovascular, cerebrovascular, or thromboembolic diseases: Y vs N	1.589 (1.097, 2.301)	0.014	1.016 (0.515, 2.002)	0.964	1.946 (1.238, 3.058)	0.004
History of diabetes: Y vs N	1.639 (1.131, 2.374)	0.009	1.040 (0.528, 2.050)	0.909	2.009 (1.278, 3.158)	0.003
ACE-I/ARB medication: Y vs N	1.587 (1.096, 2.300)	0.015	1.002 (0.508, 1.975)	0.996	1.942 (1.235, 3.054)	0.004
LDL cholesterol at baseline: > ULN vs ≤ ULN	1.586 (1.094, 2.298)	0.015	1.006 (0.510, 1.982)	0.987	1.933 (1.229, 3.040)	0.004
Time since start of dialysis	1.600 (1.104, 2.318)	0.013	1.004 (0.506, 1.994)	0.991	2.022 (1.285, 3.182)	0.002

[a]Hazard ratio is calculated using stratified Cox proportional hazards regression stratifying on region, cardiovascular history, previous ESA treatment, and adjusting on baseline Hb (continuous) and categorical covariate.
[b]Low, <25 µg DA or <5000 IU epoetin; High, ≥25 µg DA or ≥5000 IU epoetin.
Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; DA, darbepoetin alfa; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; LDL, low-density lipoprotein; N, no; ULN, upper limit of normal; Y, yes.

SUPPLEMENTAL METHODS

Study Design

Two amendments to the study protocol were introduced after the beginning of the study. Changes introduced in the first amendment (May 13, 2015) included the following: (a) a reduction of the maximum dose of roxadustat from 3.5 mg/kg to 3.0 mg/kg to align with the overall development program of roxadustat; (b) for patients randomized to receive ESAs, dosing frequencies were converted to those specified in the protocol, regardless of dosing frequencies used prior to randomization; (c) the addition of a second primary efficacy endpoint to support the submission to the United States (US) health authorities; (d) Patients' Global Impression of Change (PGIC) was included as a secondary endpoint in order to strengthen findings related to Health Related Quality of Life. Changes introduced in the second amendment (May 30, 2017) included a change in the duration of the treatment period from 104 weeks to a range of 52 to 104 weeks to align with the overall development program of roxadustat. These amendments received Independent Ethics Committee (IEC) and Institutional Review Board (IRB) approval prior to implementation.

Full Inclusion and Exclusion Criteria

Inclusion Criteria

The patient was eligible for the study if all of the following applied:

1. Patients had given written informed consent by themselves
2. Patients aged 18 years or more
3. Patients had been receiving stable chronic maintenance hemodialysis (HD), hemodiafiltration, or peritoneal dialysis (PD) with the same mode of dialysis for ≥4 months prior to randomization
4. For patients receiving HD, the vascular access had to be via native arteriovenous (AV) fistula or graft, or permanent, tunneled catheter
5. Patients were receiving intravenous (IV) or subcutaneous (SC) epoetin (ie, epoetin alfa, beta, theta, zeta, delta, or omega) or IV or SC darbepoetin alfa for ≥8 weeks prior to randomization with stable weekly doses (≤30% change from the maximum prescribed average weekly dose) during 4 weeks prior to randomization; patients on polyethylene glycol-epoetin beta were not to be included
6. Mean of the patient's three most recent hemoglobin (Hb) levels during the screening period (obtained at least 4 days apart) had to be ≥9.5 g/dL and ≤12.0 g/dL with an absolute difference ≤1.3 g/dL between the highest and the lowest value; the last Hb value had to be within 10 days prior to the randomization visit (Day 1)
7. Patients had serum ferritin of ≥100 ng/mL and transferrin saturation (TSAT) of ≥20% during the screening period
8. Patients had serum folate and serum vitamin B12 levels ≥ lower limit of normal (LLN) at screening
9. Patients' body weight (post dialysis) was between 45.0 kg and 160.0 kg
10. Female patients had to fulfill the following conditions:
    a. Non-childbearing potential female patients:
        i. Post-menopausal (defined as at least 1 year without any menses) prior to the prescreening assessments, or
        ii. Documented surgically sterile
    b. Childbearing potential female patients:
        i. Agreed not to try to become pregnant during the study and for 28 days after the final study drug administration
        ii. And had a negative pregnancy test at screening
        iii. And, if heterosexually active, agreed to consistently use two forms of highly effective birth control† (at least one of which had to be a barrier method) starting at screening and throughout the study period and for 28 days after the last study drug administration
11. Female patients had to agree not to breastfeed starting at screening and throughout the study period, and for 28 days after the final study drug administration
12. Female patients had to agree not to donate ova starting at screening and throughout the study period, and for 28 days after the final study drug administration
13. Male patients and their female spouse/partners who were of childbearing potential had to be using two forms of highly effective birth control† (at least one of which had to be a barrier

method) starting at screening and continue throughout the study period, and for 12 weeks after the final study drug administration
14. Male patients had to agree not to donate sperm starting at screening and throughout the study period, and for 12 weeks after the final study drug administration
15. Patient had to agree not to participate in another interventional study from the time of signing informed consent until the end of study visit

[†]Highly effective forms of birth control included:

- Consistent and correct usage of established oral contraception
- Injected or implanted hormonal methods of contraception
- Established intrauterine device or intrauterine system
- Barrier methods of contraception: condom or occlusive cap
- Any effective surgical sterilization

Exclusion Criteria

The patient was excluded from participation if any of the following applied:

1. Had received a red blood cell transfusion within 8 weeks prior to randomization
2. History of myelodysplastic syndrome or multiple myeloma
3. Any known hereditary hematologic disease such as thalassemia, sickle cell anemia, pure red cell aplasia, or other known causes for anemia other than chronic kidney disease
4. Any known hemosiderosis, hemochromatosis, coagulation disorder, or hyper-coagulable condition
5. Chronic inflammatory disease that could impact erythropoiesis (e.g. systemic lupus erythematosus, rheumatoid arthritis, celiac disease) even if it was currently in remission
6. An anticipated elective surgery that was expected to lead to significant blood loss during the study period or anticipated elective coronary revascularization
7. Active or chronic gastrointestinal bleeding
8. Had received any prior treatment with roxadustat or a hypoxia-inducible factor prolyl hydroxylase inhibitor
9. Had been treated with iron-chelating agents within 4 weeks prior to randomization
10. Had a history of chronic liver disease (e.g. cirrhosis or fibrosis of the liver)
11. Had known New York Heart Association Class III or IV congestive heart failure
12. Had had a myocardial infarction, acute coronary syndrome, stroke, seizure, or a thrombotic/thrombo-embolic event (e.g. deep vein thrombosis or pulmonary embolism) within 12 weeks prior to randomization
13. Had uncontrolled hypertension within 2 weeks prior to randomization
14. Hypersensitivity to epoetin alfa, darbepoetin alfa, or any of their excipients
15. Had a diagnosis or suspicion (e.g. complex kidney cyst of Bosniak Category 2F or higher) of renal cell carcinoma as shown on renal ultrasound, or another appropriate imaging method, within 12 weeks prior to randomization
16. A history of malignancy, except for 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
17. Positive for human immunodeficiency virus, hepatitis B surface antigen, or anti-hepatitis C virus antibody
18. An active clinically significant infection manifested by white blood count >ULN and/or fever, in conjunction with clinical signs or symptoms of infection within 1 week prior to randomization
19. A known untreated proliferative diabetic retinopathy, diabetic macular edema, macular degeneration, or retinal vein occlusion
20. Any prior organ transplant (that had not been explanted) or scheduled for organ transplantation
21. Participation in any interventional clinical study or had been treated with any investigational drugs within 30 days or five half-lives or limit set by national law, whichever was longer, prior to the initiation of screening
22. Had an anticipated use of dapsone in any dose amount or anticipated chronic use of acetaminophen/paracetamol >2.0 g/day during the treatment or follow-up period of the study
23. A history of alcohol or drug abuse within 2 years prior to randomization
24. Any medical condition that might have posed a safety risk to a patient in this study, may have confounded efficacy or safety assessment, or may have interfered with study participation

Study Drug Administration

Patients were instructed to take roxadustat ≥1 hour before or after their phosphate binders. One course of rescue ESA was allowed in patients taking roxadustat if the Hb level had not responded adequately (<9.0 g/dL) after ≥2 roxadustat dose increases in the previous 8 weeks, or if the roxadustat dose had reached the maximum limit. The allowed administration frequencies were once weekly, twice weekly, or TIW for epoetin alfa, and once weekly or once every other week for darbepoetin alfa, regardless of the frequency of administration prior to randomization. In addition, administration of epoetin alfa once every other week and darbepoetin alfa once every 4 weeks was allowed in patients receiving low ESA doses when considered clinically appropriate.

In the roxadustat group, during the treatment period, at any time outside the 4-weekly interval, a dose reduction was required if the rate of rise of Hb was >2 g/dL within 4 weeks, whereas a dose increase was permitted if Hb was <9.0 g/dL and no dose adjustment had occurred in the previous 4 weeks. Dosing was interrupted if Hb was ≥13 g/dL and was resumed when Hb was <12.0 g/dL.

For patients receiving roxadustat, concomitant oral iron was permitted during the study, whereas IV iron was allowed only if the patient's Hb level had not responded adequately to roxadustat after two consecutive dose increases or if the maximum dose limit had been reached, and if the patient had either ferritin <100 ng/mL or TSAT <20% or was intolerant to oral iron. For patients treated with ESA, IV iron supplementation was given according to local standard of care. The use of statins was allowed at doses not exceeding the approved maximum doses.

Assessments

MAP was calculated using systolic blood pressure (SBP) and diastolic blood pressure (DB)P measured before and after dialysis in HD patients and at only one time point in PD patients. When evaluating the time to increase in BP, an increase from baseline was defined as an increase of ≥20 mm Hg SBP and SBP ≥170 mm Hg or an increase from baseline of ≥15 mm Hg DBP and DBP ≥100 mm Hg during Weeks 1 to 36. Blood sampling for serum lipids was done under fasted conditions. All patients were required to complete the health-related quality of life (HRQoL) questionnaires (SF-36, FACT-An, EQ-5D-5L, and PGIC) either prior to or at the start of the dialysis session (HD patients) or prior to any other study assessments (PD patients).

The Short Form-36 Health Survey (SF-36) questionnaire is a tool assessing HRQoL, which includes eight domains. The SF-36 Physical Functioning (PF) domain (10 items) and the Vitality (VT) domain (four items) were included in the hierarchical testing. Scores range between 0 and 100, and higher scores indicate better health status. United States (US)-normalized values were used for the analysis where the scores normalized to the US population to have a mean of 50 and standard deviation of 10. The FACT-An includes 27 items covering four dimensions of well-being (physical, functional, social/family, and emotional), a subscale of 13 fatigue-specific items, and seven additional items related to anemia; scores range from 0 to 188, with higher scores indicating better QoL. The EQ-5D-5L consists of the EQ-5D descriptive system, which comprises five dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and the EQ visual analogue scale (VAS), which records the respondent's self-rated health status; scores range from 0 to 100, with higher scores indicating higher HRQoL. The PGIC measures the change in patients' overall status from the treatment's start; scores range from 1 (very much improved) to 7 (very much worse).

Statistical Methods

The primary European Union (EU) (European Medicines Agency [EMA]) endpoint was analyzed using the per protocol set (PPS). Based on the assumption that 80% of the randomized patients would be included in the PPS, it was calculated that randomization of 750 patients would lead to approximately 300 patients in each of the two treatment groups. This would provide 97% power to statistically demonstrate the non-inferiority of roxadustat versus ESA in the EU primary endpoint, assuming a difference (roxadustat – ESA) in Hb change from a baseline of -0.25 g/dL and a standard deviation (SD) of 1.5 g/dL. The primary US (Food and Drug Administration [FDA]) endpoint was analyzed using all randomized patients. Randomization of 750 patients would provide at least 99% power to demonstrate statistical non-inferiority of roxadustat versus ESA. For both the EU (EMA) and the US (FDA) primary efficacy endpoints, the overall one-sided significance level (alpha) was fixed at 0.025 and the non-inferiority margin was fixed to -0.75 g/dL.

The TEAE reporting period was defined as the evaluation period from the first study drug administration up to 28 days after the last dose. Additional days based on last dosing frequency was also considered in the TEAE definition.

SUPPLEMENTAL RESULTS

The mean (SD) FACT-An total score at baseline was 131.884 (29.555) in the roxadustat group and 129.470 (28.926) in the ESA group, and there were no significant differences between treatment groups in the change in total scores from baseline to the average of Weeks 12-28 (LSM difference [roxadustat – ESA], -0.128 [95% CI: -2.703, 2.447]; *P*=0.922). The mean (SD) EQ-5D-5L VAS at baseline was 64.717 (19.104) in the roxadustat group and 63.301 (18.316) in the ESA group. The mean (SD) change from baseline to the average of Weeks 12-28 in the EQ-5D-5L VAS was 3.041 (14.910) and 2.735 (14.477) in the roxadustat and ESA treatment groups, respectively. A greater proportion of patients in the roxadustat group versus the ESA group reported an improvement on the HRQoL questionnaire PGIC at each visit (eg, Week 12, 25.7% vs 16.0%; Week 36, 29.3% vs 21.7%; Week 76, 35.9% vs 25.5%).

The proportion of patients who were hospitalized was comparable in the roxadustat group (47.2%) and ESA group (45.2%), and no difference was observed in the median annual number of hospitalizations per patient (0.0 [range: 0, 45.66] vs 0.0 [range: 0, 12.23]) and in the median annual number of days of hospitalization per patient (0.0 days [range: 0.0, 365.25 days] vs 0.0 days [range: 0.0, 337.58 days]).

At each visit, mean hepcidin levels were lower in the roxadustat group compared with the ESA group, and the mean (SD) decreases in hepcidin levels from baseline were greater in the roxadustat group than in the ESA group (eg, Week 12, -12.298 [41.335] vs -6.741 [38.507]; Week 52, -32.709 [42.342] vs -17.522 [47.307]) (**Supplemental Figure S6**).