Supplementary Material

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Study Locations

This study was performed at 197 centers in 18 countries worldwide: Australia (seven centers), Bulgaria (12 centers), Canada (12 centers), Czech Republic (eight centers), Hungary (nine centers), India (14 centers), Mexico (four centers), Peru (three centers), Philippines (four centers), Poland (nine centers), Russia (14 centers), Slovakia (eight centers), Spain (eight centers), Sweden (four centers), Thailand (three centers), Ukraine (16 centers), the United States (US; 51 centers), and Vietnam (11 centers).

List of Investigators

The international coordinating investigator for this study was Steven Fishbane, MD.

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Study Committees

The sponsor ensured that reported cardiovascular events underwent proper sourcing, documentation, anonymization, blinding, and submission to the central Independent Event Review Committee (IERC) in an objective manner for the committee's adjudication. The adjudication process involved the contracting of two entities of a contract research organization: (1) the Pharmacovigilance and Safety Services that collects serious adverse events reported from the investigational sites to the Global Safety Database, and (2) the Endpoint Adjudication Committee (IERC) for the formal blinded adjudication.

Study Inclusion and Exclusion Criteria

Inclusion Criteria

1. Provision of informed consent prior to any study-specific procedures.
2. Age ≥18 years at screening Visit 1.
3. Receiving or initiating hemodialysis or peritoneal dialysis for treatment of end-stage renal disease for at least 30 days prior to randomization (modified to >2 weeks to ≤4 months following a protocol amendment to facilitate the recruitment of incident dialysis patients). Subjects treated with hemodialysis must have had access consisting of an arteriovenous (AV) fistula, AV graft, or tunneled (permanent) catheter. Subjects on peritoneal dialysis must have had a functioning peritoneal dialysis catheter in place.
4. Two central laboratory hemoglobin (Hb) values during the screening period, obtained at least 7 days apart, were to be <12 g/dL in subjects treated with an erythropoiesis-stimulating agent (ESA) at the time of enrollment or <10 g/dL in subjects not treated with an ESA at the time of enrollment. Subjects were to be considered not treated at the time of enrollment if they had not received either methoxy polyethylene glycol-epoetin beta for at least 8 weeks or any other ESA for at least 4 weeks prior to Visit 1.
5. Ferritin ≥100 ng/mL at randomization.
6. Transferrin saturation ≥20% at randomization.
7. Serum folate value ≥ lower limit of normal (LLN) at randomization.
8. Serum vitamin B12 value ≥LLN at randomization.
9. Alanine aminotransferase and aspartate aminotransferase ≤3× upper limit of normal (ULN), and total bilirubin ≤1.5×ULN at randomization.

10. Body weight 45–160 kg (prescribed dry weight).

Exclusion criteria

1. Involvement in the planning and/or conduct of the study (applied to both AstraZeneca staff and/or staff at the study center).
2. Previous randomization in the present study.
3. New York Heart Association Class III or IV congestive heart failure at enrollment.
4. Myocardial infarction, acute coronary syndrome, stroke, seizure, or a thrombotic/thromboembolic event (*e.g.,* deep vein thrombosis or pulmonary embolism) within 12 weeks prior to randomization.
5. History of chronic liver disease.
6. Known hereditary hematologic disease such as thalassemia, sickle cell anemia, a history of pure red cell aplasia, or other known causes for anemia other than chronic kidney disease.
7. Known and untreated retinal vein occlusion or known and untreated proliferative diabetic retinopathy.
8. Diagnosis or suspicion (*e.g.,* complex kidney cyst of Bosniak Category IIF, III, or IV) of renal cell carcinoma on renal ultrasound (or other imaging procedure, *e.g.,* computed tomography scan or magnetic resonance imaging) conducted at screening or within 12 weeks prior to randomization.
9. Uncontrolled hypertension at the time of randomization (defined as systolic blood pressure [BP] ≥180 mmHg or diastolic BP ≥100 mmHg on repeated measurement post-dialysis in hemodialysis subjects or at any time in peritoneal dialysis subjects), contraindication to epoetin alfa treatment (*e.g.*,

pure red cell aplasia, hypersensitivity, or known inability to tolerate epoetin alfa).

10. History of prostate cancer, breast cancer, or any other 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.
11. Positive for any of the following: human immunodeficiency virus, hepatitis B surface antigen, or anti-hepatitis C virus antibody.
12. Chronic inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, psoriatic arthritis, or inflammatory bowel disease that was determined to be the principal cause of anemia.
13. Known hemosiderosis, hemochromatosis, or hypercoagulable condition.
14. Any prior organ transplant with the exception of an autologous renal transplant or a renal transplant that was subsequently removed (“explanted”) or scheduled organ transplantation date.
15. Any red blood cell (RBC) transfusion during the screening period.
16. Any current condition leading to active significant blood loss.
17. Any prior treatment with roxadustat or a hypoxia-inducible factor-prolyl hydroxylase.
18. Had received another new chemical entity (defined as a compound that had not been approved for marketing) or had participated in any other clinical study that included drug treatment within the month preceding the first administration of the investigational product in this study.
19. History of alcohol or drug abuse within 2 years prior to randomization.

20. Females of childbearing potential, unless using contraception or sexual abstinence.
21. Pregnant or breastfeeding females.
22. Known allergy to roxadustat or epoetin alfa.
23. Any medical condition, including active, clinically significant infection, that in the opinion of the investigator or sponsor may have posed a safety risk to a subject in this study, which could have confounded safety or efficacy assessment, or could have interfered with study participation.

Permitted Concomitant Medications

Statins

When co-administered with roxadustat, statin exposure is reported to increase by 2- to 3-fold. The recommended maximum daily statin doses were: simvastatin 20 mg, atorvastatin 40 mg, rosuvastatin 10 mg, pravastatin 40 mg, fluvastatin 40 mg (20 mg if estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2), and pitavastatin 2 mg (1 mg if eGFR <30 mL/min/1.73 m^2).

Phosphate Binders

Roxadustat exposure is reduced when co-administered with phosphate binders. Patients were advised to discuss with the Investigator before changing their phosphate binder dose or dosing time. To optimize absorption of roxadustat, subjects were to take roxadustat with at least 1-hour separation from their phosphate binder.

Herbal Medicines

Use of herbal medicine during the study was strongly discouraged. All herbal and natural remedies were to be reviewed by the investigator and, if considered safe, could be continued at the same dose.

Prohibited Concomitant Medications

The following treatments/medications were prohibited during the study:

- Any other investigational drug from randomization until the end of the study
- Any erythropoietin analog during the treatment period, except for study treatment or rescue medication
- Iron-chelating agents (*e.g.,* deferoxamine/desferrioxamine, deferiprone, or deferasirox therapy) from 4 weeks prior to screening until the end of the study
- Androgens from randomization onwards until the end of the study
- Dapsone (at any dose) from randomization onwards until the end of the study
- Chronic doses of acetaminophen/paracetamol >2.0 g/day from randomization until the end of the study.

Epoetin Alfa Dosing

Epoetin alfa was administered three times weekly, unless patients were treated with epoetin alfa less frequently prior to study entry. For patients who were treated with an ESA prior to the study, the initial dose of epoetin alfa was the actual dose administered at screening. Patients who had received darbepoetin alfa or methoxy polyethylene glycol-epoetin beta prior to study entry initially received epoetin alfa at doses based on a conversion factor. A conversion ratio of x 200 was used for darbepoetin alfa based on weekly dose received at screening visit 1 (µg/week). A conversion ratio of x 70 to 80 was used for methoxy polyethylene glycol-epoetin beta based on monthly dose at screening visit 1 (µg/month).

Patients who had not received an ESA prior to the study were given an initial dose of epoetin alfa of 50 IU/kg three times a week.

Dose adjustments were made no more frequently than every 4 weeks and were consistent with the local prescribing information.

Pre-specified subgroup analyses

The prespecified subgroups for the subgroup analyses of the primary efficacy end point were:

- Age: <65 and ≥65 years; <75 and ≥75 years
- Gender: Male versus female
- Race: White; Black or African American; Asian; Native Hawaiian or other Pacific Islander; American Indian or Alaska native; other
- Weight: <70 kg vs ≥70 kg; and <100 kg vs ≥100 kg
- Weight by gender-specific median (four groups)
- Body mass index: <30 and ≥30 kg/m^2
- Geographical region: US vs ex-US
- Geographical region: North America; South America; Asia and Australia; Europe
- Dialysis type: peritoneal dialysis versus hemodialysis
- Cardiovascular/cerebrovascular/thromboembolic history: Yes or no
- Baseline Hb value: ≤10.5 g/dL and >10.5 g/dL
- Incident versus prevalent dialysis: dialysis duration ≤4 months versus >4 months from the randomization date
- Diabetes history: Yes versus no
- Epoetin alfa dose prior to randomization: ≤12,500 IU/week and >12,500 IU/week

- Baseline high-sensitivity C-reactive protein: ≤ULN versus >ULN.

Choice of Noninferiority Margin

The choice of a noninferiority (NI) margin of –0.15 for the proportion of total time interpolated Hb ≥10 g/dL was selected based on the principle of assurance that the test drug was not substantially inferior to the reference in the guidelines.[1] However, there are no regulatory guidelines in the therapeutic indication with a recommendation for an NI margin for these specific endpoints. Therefore, the NI margin of –15% was selected based on the Food and Drug Administration guideline in the urinary tract infections indication,[2] where a high responder rate was also expected and an NI margin of 15% was recommended.

The NI margin for the use of first RBC transfusion used a hazard ratio with an upper bound of the 95% confidence interval of ≤1.8. This NI margin of ≤1.8 was suggested by the US Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research.[3]

Multiple Imputation Technique

A multiple imputation analysis of covariance (ANCOVA) method was used for the primary efficacy analysis.[4] In summary, 200 datasets were generated. The data points were imputed assuming missing at random and using baseline Hb, cardiovascular history, geographical region, and dialysis duration, and the available non-missing Hb for each scheduled week as covariates, by treatment group. For each dataset, the missing monotone data points were imputed, which is when a subject misses one visit, and all subsequent visits. As a result, 200 imputed complete datasets were generated. An ANCOVA model was fitted on each of the 200 datasets where the average of the imputed and observed Hb values between weeks 28 and 52 for each patient was taken as the dependent variable, and baseline Hb, treatment group, cardiovascular history, geographical region, and dialysis duration were used as covariates. The results of all 200 ANCOVA models were combined using Rubin's rules.[5]

Overall, there were 6882 (5574 [81.0%] observed; 1308 [19.0%] imputed) and 6984 (5924 [84.8%] observed; 1060 [15.2%] imputed) datapoints for roxadustat and epoetin alfa, respectively.

Treatment Compliance

Compliance to study treatment, calculated as ([overall amount of dose actually taken] / [overall expected amount of dose to be taken]) × 100%, was also assessed (on-treatment + 7 days analysis set *i.e.,* all patients who received one dose of study treatment and censored at 7 days after treatment discontinuation). Dose taken was based on medication returned by patients to their clinics. Adequate treatment compliance was defined as ≥75%, and significant noncompliance was defined as <50%.

References

1. European Medicines Agency Guideline on the Choice of the Non-inferiority Margin. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-choice-non-inferiority-margin_en.pdf (accessed October 2020).

2. Food and Drug Administration Complicated Urinary Tract Infections and Pyelonephritis – Developing Antimicrobial Drugs for Treatment. https://www.fda.gov/media/71313/download (accessed October 2020).

3. Food and Drug Administration Guidance for Industry: Diabetes Mellitus - Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. https://www.federalregister.gov/documents/2008/12/19/E8-30086/guidance-for-industry-on-diabetes-mellitus-evaluating-cardiovascular-risk-in-new-antidiabetic (accessed October 2020).

4. O'Kelly, M.; Ratitch, B., *Clinical Trials with Missing Data: A Guide for Practitioners*. Wiley: 2014.

5. Rubin, D., *Multiple imputation for nonresponse in surveys*. Wiley: New York, 1987.

Supplemental Table 1. Initial Dosing of Roxadustat for Patients Treated with an ESA Prior to Randomization

Epoetin alfa or beta[a] (IU/week)	Darbepoetin alfa[a,b] (µg/week)	Mircera®[c] (µg/month)	Roxadustat dose[d] (mg/dose) TIW
<5000	<25	<80	70
5000 to ≤8000	25–40	80–120	100
>8000 to 16,000	>40–80	120–200	150
>16,000	>80	>200	200[e]

[a]Current weekly dose at screening Visit 1.

[b]If darbepoetin was used once every 2 weeks, half the dose given every 2 weeks was used to determine the roxadustat starting dose.

[c]Current monthly dose at screening Visit 1.

[d]Starting dose will be one step higher if the mean central Hb value from the last two screening visits is <10 g/dL.

[e]If the initial dose of 200 mg exceeded the maximum dose of 3.0 mg/kg, then 150 mg was chosen as the starting dose.

ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; TIW, three times a week.

Supplemental Table 2. Roxadustat Dose Adjustment Algorithm

Change in Hb over past 4 weeks	Hb <10.5 g/dL	Hb 10.5–11.9 g/dL	Hb 12.0–12.9 g/dL	Hb ≥13.0 g/dL
<–1.0	Dose increase	Dose increase	No change	Dose withheld and resumed when Hb was ≤11.9 g/dL, at a dose that was to be reduced by two dose steps
–1.0 to 1.0	Dose increase	No change	Dose reduction	
>1.0	No change	Dose reduction	Dose reduction	

The dose increases and reductions were pre-set according to dose steps. The dose steps were as follows: 20, 40, 50, 70, 100, 150, 200, 250, 300, and 400 mg. If patients receiving 20 mg three times a week required a dose reduction, dose frequency was reduced to twice a week. If a further dose reduction was required, frequency was reduced to once a week. The maximum dose was 3.0 mg/kg or 400 mg. If Hb increased by ≥2.0 g/dL within a 4-week period, the dose was decreased by one dose step.

Hb, hemoglobin.

Supplemental Table 3. Analysis Sets

Analysis set	Description	Endpoints analysed	Assessed for NI/superiority	NI margin	Roxadustat, *n*	Epoetin alfa, *n*
ITT	All patients randomized to study treatment throughout the duration of the study, irrespective of protocol adherence and continued participation, with the exception of patients with major Good Clinical Practice violations or system technical issues at randomization	Mean change from baseline in Hb to the average over weeks 28–52, without excluding values obtained during or following rescue therapy	NI	–0.75 g/dL	1051	1055
		Mean change in low density LDL-C from baseline to week 24	Superiority	N/A	1051	1055
		Mean change in Hb from baseline to the average over weeks 28–52 in patients with baseline hsCRP >ULN	Superiority	N/A	1051	1055
		The proportion of total time with Hb ≥10 g/dL over weeks 28–52	NI	–0.15	1051	1055
		The proportion of total time with Hb 10–12 g/dL over weeks 28–52	NI	–0.15	1051	1055
		Mean monthly IV iron use from Week 36 until EOS	Superiority	N/A	1051	1055

		Change in hepcidin from baseline until week 24	Nominal testing	N/A	1051	1055
		Change in serum iron, ferritin, TSAT and TIBC; from baseline to the mean over week 24 until EOT	Nominal testing	N/A	1051	1055
		Change in total cholesterol, HDL-C and triglycerides from baseline to the mean over week 24 until EOT	Nominal testing	N/A	1051	1055
		Change in LDL-C/HDL-C ratio from baseline to week 24	Nominal testing	N/A	1051	1055
		Change in heart rate and blood pressure from baseline to the mean over week 28 until EOT	Nominal testing	N/A	1051	1055
PPS	All randomized patients without important protocol deviations who had received at least 8 weeks of study treatment	Mean change in Hb from baseline to the average over weeks 28–36 without the need for rescue therapy	NI	–0.75 g/dL	842	869
OT+3	All patients who received at least one dose of study treatment and censored 3 days after treatment discontinuation	Use of first RBC transfusion as rescue therapy	NI	1.8	1048	1053
OT+7	All patients who received at least one dose of study	Treatment exposure, treatment compliance,	N/A	N/A	1048	1053

	treatment and censored 7 days after treatment discontinuation	serum potassium treatment-emergent values				
Safety (OT+28)	All patients who received at least one dose of study treatment and censored 28 days after treatment discontinuation	AEs, SAEs	N/A	N/A	1048	1053

AE; adverse event; EOS, end of study; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; ITT, intent-to-treat; IV, intravenous; LDL-C, low-density lipoprotein cholesterol; N/A, not applicable; NI, noninferiority;OT+3, on-treatment + 3 days; OT+7, on treatment + 7 days; OT+28, on-treatment + 28 days; PPS, per-protocol set; RBC, red blood cell; SAE, serious adverse event; TIBC, total iron binding capacity; TSAT, transferrin saturation; ULN upper level of normal.

Supplemental Table 4. Roxadustat Exposure by Dose

Dose/week	Dose, mg	Roxadustat (*n*=1048)
		Patients ever receiving, *n* (%)
1	20	133 (12.7)
1	40	1 (0.1)
1	150	1 (0.1)
2	20	197 (18.8)
2	70	1 (0.1)
3	20	305 (29.1)
3	40	425 (40.6)
3	50	603 (57.5)
3	70	842 (80.3)
3	100	821 (78.3)
3	150	657 (62.7)
3	200	318 (30.3)
3	250	110 (10.5)
3	300	36 (3.4)
3	400	7 (0.7)

On-treatment + 7 days analysis set.

Supplemental Table 5. Study Treatment Compliance

	Roxadustat (*n*=1046)	**Epoetin alfa (*n*=507)**
Mean compliance, %	97.1	96.0
Compliance (≥75% to ≤125%), *n* (%)	1009 (96.5)	477 (94.1)
Significant non-compliance (<50%), *n* (%)	9 (0.9)	12 (2.4)

On treatment + 7 days analysis set.

The percentage treatment compliance was calculated as the overall dose amount taken relative to the expected overall amount of dose to be taken. The expected amount of dose to be taken was calculated as: (overall amount of dose to be taken weekly) × (number of days between visits – number of days of planned interruption)/7. Epoetin alfa compliance was not derived for patients from the following countries as epoetin alfa was locally supplied: Australia, Brazil, Philippines, Thailand, USA, Vietnam.

Supplemental Table 6. Change in Hb (g/dL) from Baseline to Mean During Weeks 28 to 52, Sensitivity Analyses

	Roxadustat			Epoetin alfa			Difference between groups		
Pattern mixture model	**N**	**Mean baseline Hb, g/dL**	**Adjusted LSM change (95% CI/SE)**	**N**	**Baseline Hb (g/dL)**	**Adjusted LSM change (95% CI/SE)**	**Difference in LSM changes (95% CI)**	***P*-value**	**NI *P*-value**
Pattern mixture model (ITT)									
Last mean carried forward	1051	10.01	0.80 (95% CI: 0.72, 0.87)	1055	10.04	0.70 (95% CI: 0.63, 0.78)	0.09 (0.01, 0.18)	0.04	N/A
Baseline mean carried forward	1051	10.01	0.56 (95% CI: 0.48, 0.64)	1055	10.04	0.52 (95% CI: 0.44, 0.60)	0.04 (–0.05, 0.13)	0.39	N/A
Mixed model for repeated measures (ITT) without imputation									
Repeated measures analysis	1051	9.99	0.84 (SE: 0.037)	1055	10.02	0.72 (SE: 0.036)	0.11 (0.02, 0.21)	0.02	<0.001
OT+7 analysis set									
On-treatment analysis	1048	10.01	0.79 (95% CI: 0.71, 0.87)	1053	10.04	0.69 (95% CI: 0.61, 0.76)	0.10 (0.02, 0.18)	0.02	<0.001

Baseline Hb is defined as the mean of the last three central laboratory Hb values from the screening and randomization visits. For subjects without any post-baseline value, the week 2 values were initially imputed using monotone regression with the baseline Hb, incident versus prevalent dialysis (≤4 versus >4), cardiovascular/cerebrovascular/thromboembolic history and geographical region (US vs ex-US) variables. Change in Hb from baseline to mean during weeks 28 to 52 is

analyzed using an ANCOVA model with baseline Hb as covariate and cardiovascular/cerebrovascular/thromboembolic history, geographical region (US vs ex-US), incident versus prevalent dialysis (≤4 versus >4 months) and treatment group as fixed effects. Adjusted LS means, their difference, and corresponding CIs are generated from datasets where missing data are imputed using pattern mixture model-based multiple imputation with baseline Hb, incident versus prevalent dialysis (≤4 versus >4 months), cardiovascular/cerebrovascular/thromboembolic history and geographical region (US vs ex-US) as predictor variables. Subjects that died before week 28 were excluded from the analysis, and for those that died after week 28 the imputed values after death date were excluded from the analysis.

ANCOVA, analysis of covariance; CI, confidence interval; Hb, hemoglobin; ITT, intent-to-treat; LSM, least-squares mean; NI, noninferiority; OT+7, on-treatment plus 7 days; SE, standard error.

Supplemental Table 7. Results of Superiority Testing of Efficacy End Points

End point (analysis set)	Roxadustat				Epoetin alfa				Difference in LSM changes (95% CI)/HR (95% CI)[b]	Nominal *P*-value
	n	Baseline value	Final value	LSM change/ event rate[a] (total years at risk)	*n*	Baseline value	Final value	LSM change/ event rate[a] (total years at risk)		
Change in Hb from baseline to mean during weeks 28 to 52, g/dL (ITT)	1003	10.01	10.78	LSM change: 0.77	1016	10.04	10.72	LSM change: 0.68	Difference in LSM changes: 0.09 (0.01, 0.18)	0.036
Change in Hb from baseline to mean during weeks 28 to 36, g/dL (PPS)	836	9.98	10.86	LSM change: 0.88	864	10.04	10.78	LSM change: 0.74	Difference in LSM changes: 0.14 (0.03, 0.25)	0.012
Proportion of total time of interpolated Hb ≥10 g/dL from week 28 to 52[c] (ITT)	896	NA	NA	Adjusted LSM : 0.79	941	NA	NA	Adjusted LSM : 0.76	Difference in LSM: 0.03 (0.00, 0.05)	0.045
Proportion of total time of interpolated Hb values between 10 to 12 g/dL from week 28 to 52[c] (ITT)	896	NA	NA	Adjusted LSM : 0.65	941	NA	NA	Adjusted LSM : 0.63	Difference in LSM : 0.02 (–0.01, 0.05)	0.130
Event rate for first RBC transfusion (OT+3)	1048	NA	NA	Event rate: 6.0 (1716.4)	1053	NA	NA	Event rate: 7.2 (1920.1)	HR: 0.83 (0.64, 1.07)	0.151

[a]Rate of RBC transfusion per 100 patient-years.

[b]HR (95% CI) comparing risk of RBC transfusion for roxadustat versus epoetin alfa.

[c]Proportion of total time of interpolated Hb values ≥10 or 10–12 g/dL was calculated as the time the linearly interpolated curve between measurements was ≥10 or 10–12 g/dL, respectively, divided by the time between measurements from week 28 to 52.

CI, confidence interval; Hb, hemoglobin; HR, hazard ratio; ITT, intent-to-treat; LSM, least-squares mean; OT+3, on-treatment plus 3 days; PPS, per-protocol set; RBC red blood cell.

Supplemental Table 8. Change in Lipid Parameters From Baseline*

End point	Roxadustat (*n*=1051)			Epoetin alfa (*n*=1055)			LSM treatment difference (95% CI)	*P*-value
	n	Mean baseline	Adjusted LSM (95% CI)	*n*	Mean baseline	Adjusted LSM (95% CI)		
Total cholesterol, mg/dL	916	165.21	–24.47 (–26.80, –22.14)	963	165.62	–5.33 (–7.61, –3.04)	–19.14 (–21.81, –16.47)	<0.001
HDL-C, mg/dL	915	44.93	–4.75 (–5.50, –4.00)	961	45.93	–1.15 (–1.89, –0.41)	–3.60 (–4.46, –2.74)	<0.001
LDL-C/HDL-C ratio	871	2.10	–0.22 (–0.28, –0.15)	924	2.06	–0.03 (–0.09, 0.04)	–0.19 (–0.27, –0.11)	<0.001
Triglycerides, mg/dL	916	163.92	–13.02 (–19.19, –6.84)	962	161.14	–6.70 (–12.74, –0.65)	–6.32 (–13.39, 0.75)	0.080

*Change from baseline to the mean of week 24 to EOT in total cholesterol, HDL-C and triglycerides. LDL-C/HDL-C is the change from baseline to Week 24. Intent-to-treat analysis set. Change from baseline to mean during week 24 to EOT visit was analyzed using an ANCOVA model with baseline value for respective lipid and baseline Hb as covariates and cardiovascular/cerebrovascular/thromboembolic history, geographical region (US versus ex-US), incident versus prevalent dialysis (≤4 versus >4 months), and treatment group as fixed effects. Baseline was defined as the last measurement prior to randomization.

ANCOVA, analysis of covariance; CI, confidence interval; EOT, end of treatment; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LSM, least-squares means.

Supplemental Table 9. SAEs Within the Cardiac Disorders System Organ Class by SAE Term

SAE category	Roxadustat (*n*=1048)			Epoetin alfa (*n*=1053)		
	***N* pts w/ event**	**%**	***N* per 100 P-Y**	***N* pts w/ event**	**%**	***N* per 100 P-Y**
Acute myocardial infarction	39	3.7	2.1	41	3.9	2.0
Cardiac failure congestive	24	2.3	1.3	29	2.8	1.4
Coronary artery disease	17	1.6	0.9	16	1.5	0.8
Myocardial infarction	14	1.3	0.8	6	0.6	0.3
Cardiac failure	13	1.2	0.7	10	0.9	0.5
Atrial fibrillation	10	1.0	0.5	18	1.7	0.9
Cardiac failure acute	10	1.0	0.5	5	0.5	0.2
Angina pectoris	8	0.8	0.4	8	0.8	0.4
Cardio-respiratory arrest	7	0.7	0.4	4	0.4	0.2
Bradycardia	6	0.6	0.3	2	0.2	0.1
Acute coronary syndrome	6	0.6	0.3	1	<0.1	0.1
Angina unstable	5	0.5	0.3	6	0.6	0.3
Myocardial ischemia	4	0.4	0.2	6	0.6	0.3
Cardiac arrest	3	0.3	0.2	7	0.7	0.3
Ventricular fibrillation	3	0.3	0.2	4	0.4	0.2
Arrhythmia	3	0.3	0.2	3	0.3	0.1
Arteriosclerosis coronary artery	3	0.3	0.2	0	0.0	0.0
Atrioventricular block	3	0.3	0.2	0	0.0	0.0
Cardiopulmonary failure	2	0.2	0.1	4	0.4	0.2
Acute left ventricular failure	2	0.2	0.1	3	0.3	0.1
Cardiogenic shock	2	0.2	0.1	2	0.2	0.1
Aortic valve stenosis	2	0.2	0.1	0	0.0	0.0
Atrial flutter	2	0.2	0.1	0	0.0	0.0
Cardiac tamponade	2	0.2	0.1	0	0.0	0.0
Cardiac failure chronic	1	<0.1	0.1	5	0.5	0.2
Pulseless electrical activity	1	<0.1	0.1	2	0.2	0.1
Left ventricular dysfunction	1	<0.1	0.1	1	<0.1	0.1
Left ventricular failure	1	<0.1	0.1	1	<0.1	0.1
Pericarditis	1	<0.1	0.1	1	<0.1	0.1
Trifascicular block	1	<0.1	0.1	1	<0.1	0.1

Atrial tachycardia	1	<0.1	0.1	0	0.0	0.0
Atrial thrombosis	1	<0.1	0.1	0	0.0	0.0
Atrioventricular dissociation	1	<0.1	0.1	0	0.0	0.0
Cardiac disorder	1	<0.1	0.1	0	0.0	0.0
Bundle branch block left	1	<0.1	0.1	0	0.0	0.0
Cardiac valve disease	1	<0.1	0.1	0	0.0	0.0
Cardiomegaly	1	<0.1	0.1	0	0.0	0.0
Cardiovascular disorder	1	<0.1	0.1	0	0.0	0.0
Cor pulmonale acute	1	<0.1	0.1	0	0.0	0.0
Hypertensive heart disease	1	<0.1	0.1	0	0.0	0.0
Nodal arrythmia	1	<0.1	0.1	0	0.0	0.0
Palpitations	1	<0.1	0.1	0	0.0	0.0
Pericarditis uremic	1	<0.1	0.1	0	0.0	0.0
Sinus bradycardia	1	<0.1	0.1	0	0.0	0.0
Tachyarrhythmia	1	<0.1	0.1	0	0.0	0.0
Tachycardia	1	<0.1	0.1	0	0.0	0.0
Tachycardia paroxysmal	1	<0.1	0.1	0	0.0	0.0
Tricuspid valve disease	1	<0.1	0.1	0	0.0	0.0
Ventricular arrhythmia	1	<0.1	0.1	0	0.0	0.0
Ventricular hypokinesia	1	<0.1	0.1	0	0.0	0.0
Sinus node dysfunction	0	0.0	0.0	4	0.4	0.2
Ventricular tachycardia	0	0.0	0.0	4	0.4	0.2
Right ventricular failure	0	0.0	0.0	3	0.3	0.1
Cardiovascular insufficiency	0	0.0	0.0	2	0.2	0.1
Coronary artery stenosis	0	0.0	0.0	2	0.2	0.1
Pericardial effusion	0	0.0	0.0	2	0.2	0.1
Aortic valve incompetence	0	0.0	0.0	1	<0.1	0.1
Atrioventricular block complete	0	0.0	0.0	1	<0.1	0.1
Cardiac asthma	0	0.0	0.0	1	<0.1	0.1
Cardiac perforation	0	0.0	0.0	1	<0.1	0.1
Congestive cardiomyopathy	0	0.0	0.0	1	<0.1	0.1
Intracardiac thrombus	0	0.0	0.0	1	<0.1	0.1
Ischemic cardiomyopathy	0	0.0	0.0	1	<0.1	0.1
Mitral valve incompetence	0	0.0	0.0	1	<0.1	0.1
Supraventricular extrasystoles	0	0.0	0.0	1	<0.1	0.1
Supraventricular tachycardia	0	0.0	0.0	1	<0.1	0.1
Ventricular extrasystoles	0	0.0	0.0	1	<0.1	0.1

On-treatment + 28 days analysis set. All SAEs are listed in the clinical trials.gov listing for this study (https://clinicaltrials.gov/ct2/show/results/NCT02174731).

P-Y, patient-years; SAE, serious adverse event; w/, with.

Supplemental Table 10. AEs Leading to Discontinuation of Study Medication by AE Term

AE category	Roxadustat (*n*=1048)			Epoetin alfa (*n*=1053)		
	***N* pts w/ event**	**%**	***N* per 100 P-Y**	***N* pts w/ event**	**%**	***N* per 100 P-Y**
Nausea	5	0.5	0.27	0	0	0
Death	3	0.3	0.16	3	0.3	0.14
Acute myocardial infarction	3	0.3	0.16	1	<0.1	0.05
Diarrhea	3	0.3	0.16	0	0	0
Sepsis	3	0.3	0.16	0	0	0
End-stage renal disease	2	0.2	0.11	1	<0.1	0.05
Peritonitis	2	0.2	0.11	0	0	0
Hypertension	2	0.2	0.11	0	0	0
Cerebral hemorrhage	1	<0.1	0.05	1	<0.1	0.05
Hemorrhagic stroke	1	<0.1	0.05	1	<0.1	0.05
Hemoglobin decreased	1	<0.1	0.05	1	<0.1	0.05
Bacterial sepsis	1	<0.1	0.05	0	0	0
Gangrene	1	<0.1	0.05	0	0	0
Hepatitis C	1	<0.1	0.05	0	0	0
Septic shock	1	<0.1	0.05	0	0	0
Colon cancer metastatic	1	<0.1	0.05	0	0	0
Endometrial adenocarcinoma	1	<0.1	0.05	0	0	0
Gastrointestinal carcinoma	1	<0.1	0.05	0	0	0
Cerebral infarction	1	<0.1	0.05	0	0	0
Headache	1	<0.1	0.05	0	0	0
Ischemic stroke	1	<0.1	0.05	0	0	0
Cardiac failure	1	<0.1	0.05	0	0	0
Cardiac failure congestive	1	<0.1	0.05	0	0	0
Cardiac tamponade	1	<0.1	0.05	0	0	0
Cardio-respiratory arrest	1	<0.1	0.05	0	0	0

Cardiovascular disorder	1	<0.1	0.05	0	0	0
Palpitations	1	<0.1	0.05	0	0	0
Deep vein thrombosis	1	<0.1	0.05	0	0	0
Hypertensive crisis	1	<0.1	0.05	0	0	0
Hypertensive emergency	1	<0.1	0.05	0	0	0
Vasculitis	1	<0.1	0.05	0	0	0
Cough	1	<0.1	0.05	0	0	0
Dyspnea	1	<0.1	0.05	0	0	0
Pulmonary embolism	1	<0.1	0.05	0	0	0
Pulmonary fibrosis	1	<0.1	0.05	0	0	0
Respiratory failure	1	<0.1	0.05	0	0	0
Abdominal discomfort	1	<0.1	0.05	0	0	0
Anal ulcer	1	<0.1	0.05	0	0	0
Constipation	1	<0.1	0.05	0	0	0
Enterocutaneous fistula	1	<0.1	0.05	0	0	0
Hemorrhoids	1	<0.1	0.05	0	0	0
Inflammatory bowel disease	1	<0.1	0.05	0	0	0
Pancreatitis	1	<0.1	0.05	0	0	0
Small intestinal obstruction	1	<0.1	0.05	0	0	0
Vomiting	1	<0.1	0.05	0	0	0
Hepatic steatosis	1	<0.1	0.05	0	0	0
Hepatitis toxic	1	<0.1	0.05	0	0	0
Hepatobiliary disease	1	<0.1	0.05	0	0	0
Hyperhidrosis	1	<0.1	0.05	0	0	0
Rash	1	<0.1	0.05	0	0	0
Rash maculo-papular	1	<0.1	0.05	0	0	0
Fibromyalgia	1	<0.1	0.05	0	0	0
Azotemia	1	<0.1	0.05	0	0	0
Renal failure	1	<0.1	0.05	0	0	0
Fatigue	1	<0.1	0.05	0	0	0
Hepatic enzyme increased	1	<0.1	0.05	0	0	0
Delayed graft function	1	<0.1	0.05	0	0	0
HIV infection	0	0	0	1	<0.1	0.05

Pneumonia	0	0	0	1	<0.1	0.05
Adenocarcinoma of colon	0	0	0	1	<0.1	0.05
Lung carcinoma cell type unspecified stage IV	0	0	0	1	<0.1	0.05
Esophageal carcinoma	0	0	0	1	<0.1	0.05
Aplasia pure red cell	0	0	0	1	<0.1	0.05
Bone marrow reticulin fibrosis	0	0	0	1	<0.1	0.05
Adult failure to thrive	0	0	0	1	<0.1	0.05
Decreased appetite	0	0	0	1	<0.1	0.05
Cerebrovascular accident	0	0	0	1	<0.1	0.05
Dementia	0	0	0	1	<0.1	0.05
Spinal cord compression	0	0	0	1	<0.1	0.05
Cardiopulmonary failure	0	0	0	1	<0.1	0.05
Myocardial infarction	0	0	0	1	<0.1	0.05
Swelling face	0	0	0	1	<0.1	0.05
General physical health deterioration	0	0	0	1	<0.1	0.05
Body temperature increased	0	0	0	1	<0.1	0.05
Subarachnoid hemorrhage	0	0	0	1	<0.1	0.05

On-treatment + 28 days analysis set.

AE, adverse event; P-Y, patient-years; w/, with.

Supplemental Table 11. Change in Heart Rate and Blood Pressure From Baseline to Mean Over Week 28 to End of Treatment

Outcome	Roxadustat (*n*=1051)			Epoetin alfa (*n*=1055)			LSM treatment difference	*P* value
	n	Mean baseline	LSM change	*n*	Mean baseline	LSM change		
Sitting systolic blood pressure (mmHg)	841	140.83	0.86 (–0.21, 1.94)	921	140.37	1.06 (0.03, 2.09)	–0.19 (–1.38, 0.99)	0.748
Sitting diastolic blood pressure (mmHg)	841	78.23	–0.68 (–1.27, –0.09)	921	77.76	–0.03 (–0.60, 0.54)	–0.65 (–1.31, 0.00)	0.050
Mean arterial pressure (mmHg)	841	99.10	–0.18 (–0.86, 0.50)	921	98.63	0.29 (–0.36, 0.95)	–0.48 (–1.22, 0.27)	0.214
Heart rate (beats/min)	841	75.26	–0.47 (–1.02, 0.08)	921	75.75	–0.30 (–0.83, 0.23)	–0.17 (–0.78, 0.44)	0.582

Intent-to-treat analysis set.

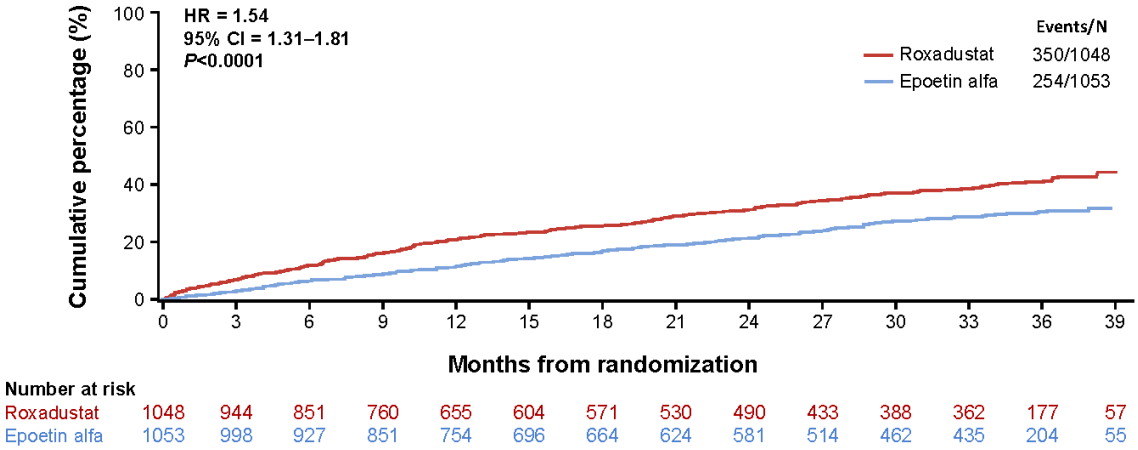
LSM, least-squares mean.

Supplemental Table 12. Serum Potassium Treatment-Emergent Laboratory Values

Outcome, *n* (%)	Roxadustat (*n*=1048)	Epoetin alfa (*n*=1053)
Serum potassium, mmol/L		
≤3.5	284 (27.1)	333 (31.6)
≥6.0	446 (42.6)	482 (45.8)
≥6.5	249 (23.8)	262 (24.9)
≥7.0	127 (12.1)	150 (14.2)

Subjects are included in a category if they have at least one post-baseline value fulfilling the criteria. On-treatment + 7 days analysis set.

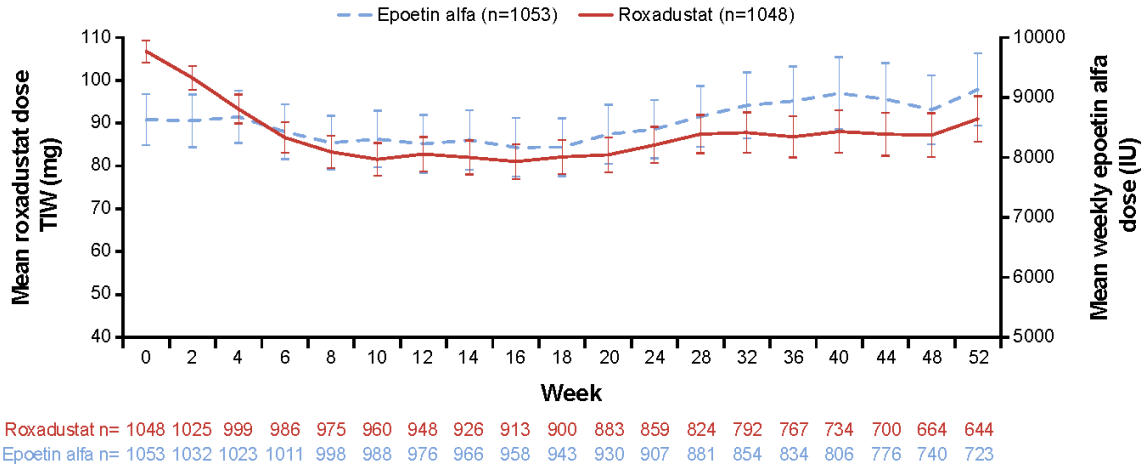
Supplemental Figure 1. Study Drug Discontinuation



On-treatment + 28 days analysis set. HR was calculated *post hoc*. Permanent discontinuation criteria for the roxadustat arm: patient decision or investigator decision (adverse event, severe non-compliance, need for >1 cycle of erythropoiesis-stimulating agent rescue, and organ transplantation).

CI, confidence interval; HR, hazard ratio.

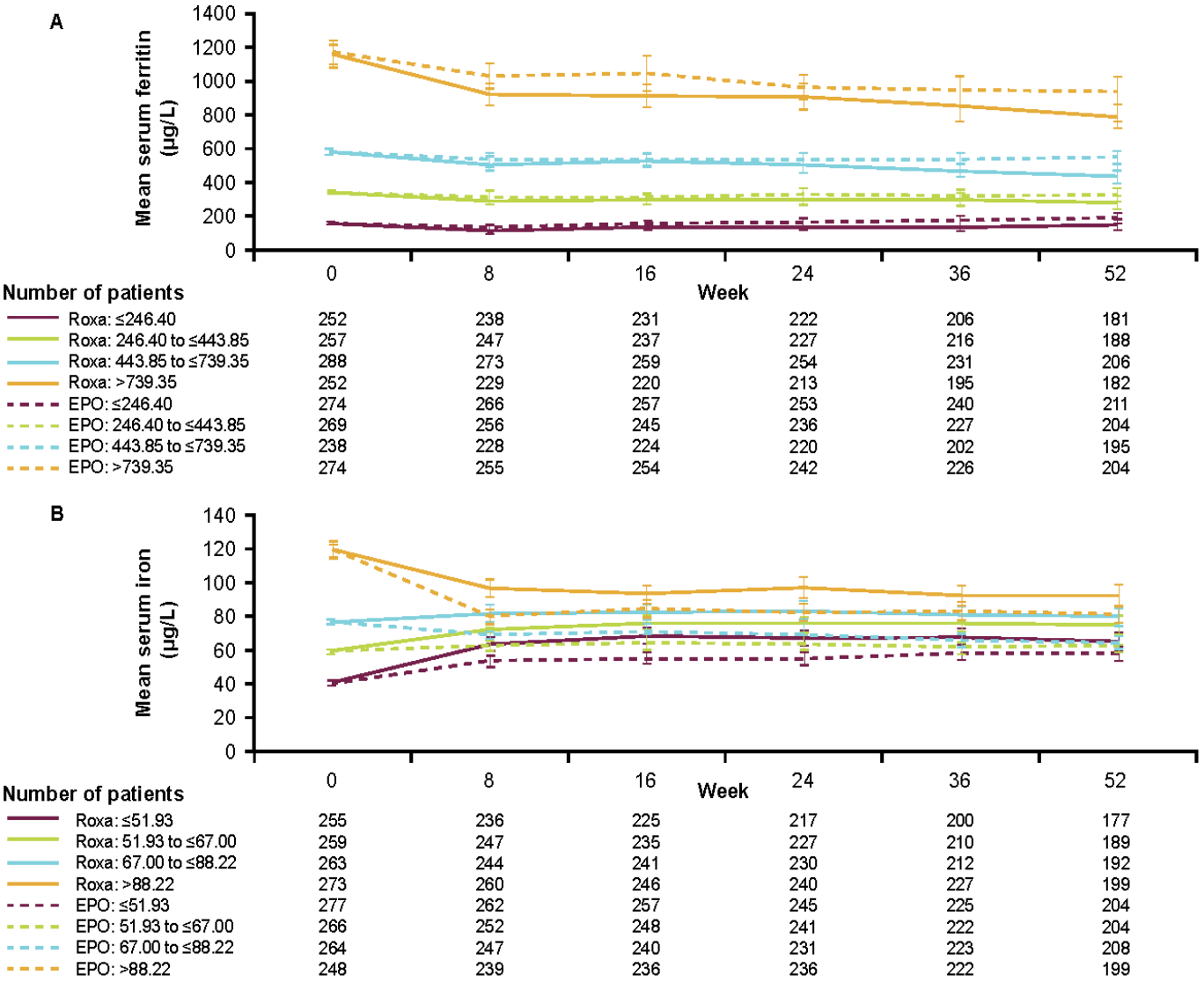
Supplemental Figure 2. Mean Weekly Dose of Roxadustat and Epoetin Alfa to Week 52

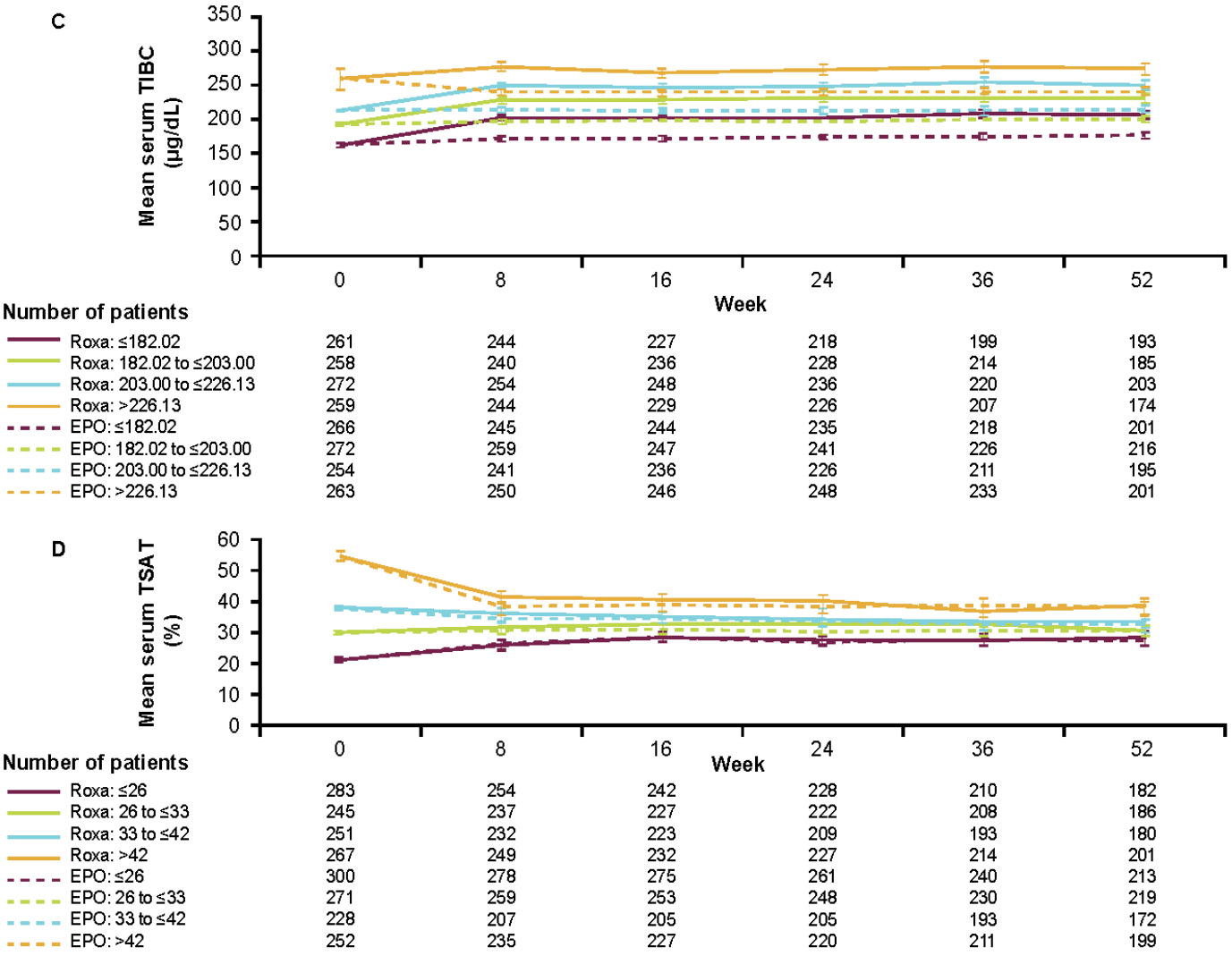


On-treatment + 7 days analysis set. Error bars are 95% confidence intervals. TIW dose-equivalent included for patients receiving roxadustat weekly or twice weekly. Maximum dose capped at 3.0 mg/kg per dose administration.

TIW, three times a week.

Supplemental Figure 3. Serum Iron Parameters by Visit, According to Baseline Quartile. A) Ferritin; B) Iron; C) TIBC; D) TSAT





Intent-to-treat analysis set. Error bars are 95% CIs. Baseline is defined as the last measurement prior to randomization. 95% CI of the mean is based on the normal distribution.

CI, confidence interval; EPO, epoetin alfa; Roxa, roxadustat; TIBC, total iron binding capacity; TSAT, transferrin saturation.