Supplementary Material

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Study locations and investigators

This study was performed at 385 centers in 25 countries worldwide: Argentina (18 centers), Brazil (19 centers), Bulgaria (11 centers), Canada (22 centers), Colombia (4 centers), Czech Republic (10 centers), Germany (3 centers), Hungary (13 centers), India (23 centers), Korea (13 centers), Malaysia (4 centers), Mexico (8 centers), Peru (11 centers), Philippines (5 centers), Poland (7 centers), Romania (6 centers), Russia (20 centers), Slovakia (6 centers), Spain (7 centers), Taiwan (10 centers), Thailand (7 centers), Turkey (8 centers), Ukraine (25 centers), United States (US; 113 centers), and Vietnam (12 centers).

In addition, 54 centers were opened but did not contribute any patients to the study analyses.

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Inclusion criteria

- Provision of informed consent prior to any study-specific procedures.
- Age ≥18 years at screening Visit 1.
- Estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 (calculated by central laboratory using the 4-variable Modification of Diet in Renal Disease [MDRD] equation) corresponding to stage 3–5 chronic kidney disease (CKD) according to the Kidney Disease Outcomes Quality Initiative, not receiving dialysis.[1, 2]
- Mean of two most recent central laboratory hemoglobin values during the screening period, obtained at least 7 days apart, had to be <10.0 g/dL.
- Ferritin ≥50 ng/mL at randomization (obtained from screening visit).
- Transferrin saturation (TSAT) ≥15% at randomization (obtained from the screening visit).
- Serum folate level greater than or equal to the lower limit of normal (LLN) at randomization (obtained from the screening visit).
- Serum vitamin B12 level greater than or equal to the LLN at randomization (obtained from the screening visit).
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3 × upper limit of normal (ULN) and total bilirubin ≤1.5 × ULN at randomization (obtained from the screening visit).
- Body weight of 45–160 kg.

Exclusion criteria

- Involvement in the planning and/or conduct of the study.
- Previous randomization in the current study.
- Any erythropoiesis-stimulating agent (ESA) treatment within 6 weeks of randomization.
- New York Heart Association Class III or IV congestive heart failure at enrollment.
- 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.
- History of chronic liver disease (*e.g.,* chronic infectious hepatitis, chronic autoimmune liver disease, cirrhosis or fibrosis of the liver).
- 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 CKD.
- Known and untreated retinal vein occlusion or known and untreated proliferative diabetic retinopathy (risk for retinal vein thrombosis).
- 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.
- Systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥95 mmHg (confirmed by repeated measurement), within 2 weeks prior to randomization. Patients could be rescreened once blood pressure was controlled.

- 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.
- Positive for any of the following: human immunodeficiency virus, hepatitis B surface antigen, or anti-hepatitis C virus antibody.
- Chronic inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, psoriatic arthritis, or inflammatory bowel disease that were determined to be the principal cause of anemia.
- Known hemosiderosis, hemochromatosis, or hypercoagulable condition.
- Any prior organ transplant or a scheduled organ transplantation date.
- Any red blood cell (RBC) transfusion during the screening period.
- Any current condition leading to active significant blood loss.
- Any treatment with roxadustat or a hypoxia-inducible factor prolyl hydroxylase inhibitor.
- Had received another new chemical entity (defined as a compound which had not been approved for marketing) or had participated in any other clinical study that included drug treatment within at least 1 month of the first administration of the study drug in this study. (Note: patients consented and screened, but not randomized in this study or a previous study were not excluded.)
- History of alcohol or drug abuse within 2 years prior to randomization.
- Females of childbearing potential, unless using contraception or sexual abstinence.
- Pregnant or breastfeeding females.
- Known allergy to the investigation product or any of its ingredients.

- Any medical condition, including active, clinically significant infection, which in the opinion of the Investigator or Sponsor could have posed a safety risk to a patient in this study, which may have confounded safety or efficacy assessment or might have interfered with study participation.

Dose adjustment algorithm

Dose adjustments were permitted starting at week 4 and at intervals of every 4 weeks until week 52, and every 8 weeks thereafter using a dose adjustment algorithm. All dose adjustments were based on hemoglobin values using Hemocue, a point of care device. Hemoglobin values were to be recorded in the electronic case report form and the Interactive Web Response System.

Change in Hb over past 4 weeks[a]	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 ≤11.9 g/dL, at a dose that was reduced by two dose steps
–1.0 to 1.0	↑	No change	↓	
>1.0	No change	↓	↓	

[a]After week 52, dose to be adjusted based on current hemoglobin (Hb) (increase 1 dose step if <10.5 g/dL, no change if 10.5 to 11.9 g/dL, or decrease 1 dose step if 12 to 12.9 g/dL).

Dose increases and reductions:

Dose increases and reductions were preset according to dose steps. Dose steps were as follows: 20, 40, 50, 70, 100, 150, 200, 250, and 300 mg. Example: A dose increase at a dose of 70 mg would result in 100 mg as the new dose. A dose reduction at a dose of 150 mg would result in 100 mg as the new dose. If patients on 20 mg three times weekly required a dose reduction, frequency was to be reduced to twice a week, *i.e.,* 20 mg administered twice a week. If further dose reductions were needed, frequency was to be reduced to once weekly, *i.e.,* 20 mg administered once a week. Note: The maximum dose was capped at the lower of 3.0 mg/kg or 300 mg per dose administration.

Dose adjustment for excessive erythropoiesis:

If hemoglobin increased by >2.0 g/dL within a 4-week period, the dose was to be reduced by 1 step. The dose could be adjusted at any time, even on visits without a dose adjustment review. In such cases, dose adjustment reviews were then resumed at 4-week intervals until week 52, thereafter at 8-week intervals. If a dose adjustment review was performed on Week 18, then the next dose adjustment review was to be scheduled on week 24, since there was no scheduled visit on week 22.

Prohibited medication

The following medications/therapies were prohibited during the study:

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

Rescue medication

Intravenous (IV) iron:

Oral iron supplementation was allowed for both treatment arms without restriction. Oral iron was recommended for dietary supplementation to support erythropoiesis and as the first line for prevention and treatment of iron deficiency, unless the patient was intolerant to this treatment. Use of IV iron was not encouraged. However, the Investigator could initiate the use of an approved IV iron supplement if:

- The patient was receiving or did not tolerate oral iron, and
- Hemoglobin <8.5 g/dL, and
- Ferritin <100 ng/mL or TSAT <20%.

Treatment with the study drug could continue during IV iron administration. Ferritin and TSAT assessment were recommended 4 weeks after IV iron administration. Discontinuation of IV iron supplementation was recommended once the patient was no longer considered to be iron deficient (ferritin ≥100 ng/mL and TSAT ≥20%) or hemoglobin >9 g/dL, whichever occurred first.

RBC transfusion:

RBC transfusion was allowed if rapid correction of anemia was required to stabilize the patient's condition (*e.g.,* acute hemorrhage) or the Investigator was of the opinion that blood transfusion was a medical necessity. Investigational product treatment was allowed to continue during or after RBC transfusion administration.

Erythropoiesis-stimulating agents (ESA):

The Investigator could use an approved ESA as rescue medication if all of the following criteria were met:

- A patient's hemoglobin level had not sufficiently responded to two or more dose increases or the maximum dose limit of the study drug had been reached, and
- The patient's hemoglobin was <8.0 g/dL on two consecutive measurements drawn at least 5 days apart, and
- Clinical judgment did not suggest iron deficiency or bleeding as a cause of lack of response or rapid decline in hemoglobin, and
- Reducing the risk of alloimmunization in transplant eligible patients and/or reduction of other RBC transfusion-related risks was a goal.

Patients were not allowed to be administered both an ESA and the study drug at the same time. Patients could receive two cycles of rescue treatment with ESA. If they met the above criteria for ESA rescue for a third time, the study drug was to be permanently discontinued. In addition, the study drug was to be permanently discontinued for patients who initiated dialysis and who were clinically judged to require ESA therapy.

Missing at random-based multiple imputation analysis of covariance

Non-monotone missing Hb data points (where patients skipped intermediate visits but returned for subsequent visits) were imputed assuming missing at random using the Markov Chain Monte Carlo (MCMC) model and using baseline Hb, eGFR, cardiovascular history, geographical region, 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 patient missed one visit, and all subsequent visits. As a result, 200 imputed complete datasets were generated. An analysis of covariance (ANCOVA) model was fitted on each of the 200 datasets, where the average of the imputed and observed Hb values between weeks 28 to 52 for each patient was taken as the dependent variable and baseline Hb, baseline eGFR, treatment group, cardiovascular history, and geographical region were used as covariates. The results of all 200 ANCOVA models were combined using Rubin's rules.[3]

Efficacy subgroup analyses

Subgroup analyses were performed on the primary efficacy endpoint, using the ITT analysis set and the following key patient subgroups:

- Hemoglobin: ≤8 and >8 g/dL, and ≤9 and >9 g/dL.
- Age: <65 and ≥65 years.
- Sex: Male versus Female.
- Race: White, Black or African American, Asian, American Indian or Alaska native, Other.
- Baseline weight: <70 kg versus ≥70 kg.
- Geographical region: US versus ex-US.
- Baseline eGFR value: <30 versus ≥30, <15 versus ≥15, and <10 versus ≥10 mL/min/1.73 m^2.
- Diabetes history: Yes versus No.
- Baseline iron repletion status (ferritin >100 and TSAT >20%): Yes versus No.

Treatment compliance

Treatment compliance was calculated as follows:

([Overall amount of dose actually taken] / [overall expected amount of dose to be taken]) × 100%

Dose taken was calculated based on medication returned by patients to their clinics. Low compliance and significant noncompliance were determined as <75% and <50%, respectively.

Supplemental Table 1. Statistical analyses of secondary efficacy end points

Fixed sequence number[a]	Secondary efficacy end point	Analysis population	Statistical methods
1	Hb response	FAS	Hb response (Yes/No) at two consecutive visits (with available data) separated by at least 5 days during the first 24 weeks of treatment without having received rescue therapy prior to Hb response. The first date of the consecutive visits was to be used as the date of response. The second date of the two consecutive visits was to be used when evaluating the presence or absence of rescue therapy. The proportion of responders was compared using a Cochran-Mantel-Haenszel test adjusting for geographic region, cardiovascular history, baseline Hb (≤8, >8 g/dL), and baseline eGFR (≤30, >30 mL/min/1.73 m^2), for roxadustat compared with placebo
2	Mean change in Hb from baseline averaged over Weeks 28–52 among patients with baseline hsCRP greater than the ULN	ITT	Analyzed analogously as the primary efficacy endpoint. Superiority of roxadustat compared with placebo was declared if the lower bound of the two-sided 95% CI of the difference between roxadustat and placebo exceeded 0
3	Proportion of total time of interpolated Hb values ≥10 g/dL from Weeks 28 to 52		ANCOVA with treatment arm, geographic region, and cardiovascular history as fixed effects, and baseline Hb and baseline eGFR as covariates. Superiority of roxadustat compared with placebo was declared if the lower bound of the two-sided CI of the difference between roxadustat and placebo exceeded 0
4	Proportion of total time of interpolated Hb values 10–12 g/dL from Weeks 28 to 52		
5	Mean change from baseline in LDL cholesterol to Week 24		ANCOVA with treatment arm, geographic region and cardiovascular history as fixed effects, and baseline values for Hb, eGFR, and LDL cholesterol as covariates. Superiority of roxadustat compared with placebo was declared if the upper bound of the two-sided 95% CI of the difference between roxadustat and placebo exceeded 0
6	Need for first rescue therapy (composite) of any of IV iron, RBC transfusion, or ESA as rescue therapy	OT+28	Cox proportional hazard model. Baseline Hb, baseline eGFR, geographic region, and cardiovascular history were included as covariates. Superiority of roxadustat compared with placebo was declared if the upper limit of the two-sided 95% CI for

7	Need for first RBC transfusion as rescue therapy		the HR was ≤1.0. The first rescue therapy end points are presented as the number (%) of patients with the event and event rates per 100 patient-years at risk (total number of years at risk)
8	Mean change in SF-36 Vitality sub-score from baseline averaged over Weeks 12–28	ITT	MMRM with treatment, visit, treatment-by-visit interaction and baseline covariates, including the baseline score, baseline Hb, baseline eGFR, geographic region, and cardiovascular history as fixed effects, and patient as a random effect. Superiority of roxadustat compared with placebo was declared if the lower bound of the two-sided CI for the difference between roxadustat and placebo exceeded 0
9	Annual rate of eGFR change prior to initiation of dialysis/kidney transplant		MMRM using all post-baseline eGFR values prior to initiation of dialysis/transplant. Baseline eGFR, baseline Hb, geographic region, cardiovascular history, treatment arm, and post-baseline eGFR measurement time were used as fixed effects, and patient and time as random effects, *i.e.,* random intercept and slope
10	Mean change in SF-36 Physical Functioning sub-score from baseline averaged over Weeks 12–28		MMRM with treatment, visit, treatment-by-visit interaction, and baseline covariates, including the baseline score, baseline Hb, baseline eGFR, geographic region, and cardiovascular history as fixed effects, and patient as a random effect. Superiority of roxadustat compared with placebo was declared if the lower bound of the two-sided CI for the difference between roxadustat and placebo exceeded 0. The formal hypothesis testing would stop regardless of the testing result

[a]Formal statistical hypothesis testing was stopped as soon as a test was accompanied by a *P*-value ≥0.05.

ANCOVA, analysis of covariance; CI, confidence interval; eGFR, estimated glomerular filtration rate; FAS, full analysis set; Hb, hemoglobin; HR, hazard ratio; ESA, erythropoiesis-stimulating agent; hsCRP, high-sensitivity C-reactive protein; ITT, intent-to-treat; IV, intravenous; LDL, low-density lipoprotein; MMRM, mixed-effect model repeated measure; RBC, red blood cell; SF, short-form; ULN, upper limit of normal.

Supplemental Table 2. Statistical analyses of exploratory efficacy end points

Exploratory efficacy end point	Analysis population	Statistical methods
Change in serum iron profiles: ferritin, total iron binding capacity, and transferrin saturation from baseline throughout week 24 to EOT visit	ITT	ANCOVA with baseline Hb, baseline eGFR, baseline value, treatment, cardiovascular history, and geographic region as covariates
Change from baseline in hepcidin to week 24		
Time to initiation of dialysis	OT+28	Cox proportional hazard model. Baseline Hb, baseline eGFR, geographic region, and cardiovascular history were included as covariates. Time to initiating dialysis was calculated as (date of first initiation of dialysis, or date of censoring if no dialysis was initiated) – (date of randomization) + 1. Patients who did not initiate dialysis but had a renal transplant were censored at the date of transplant. Patients who did not initiate dialysis and did not have a renal transplant were censored at the earliest date of the EOS visit, or if treatment was stopped prior to the end of the treatment visit, the date of last contact or withdrawal of consent, or date of death
Change in blood pressure (systolic blood pressure and diastolic blood pressure) from baseline throughout week 28 to EOT visit	ITT	Conducted using ANCOVA

ANCOVA, analysis of covariance; eGFR, estimated glomerular filtration rate; EOS, end of study; EOT, end of treatment; Hb, hemoglobin; ITT, intent-to-treat.

Supplemental Table 3. Key medications taken during study treatment

Medication, *n* (%)	Roxadustat (*n*=1384)	Placebo (*n*=1377)
Iron supplements	869 (62.8)	908 (65.9)
Iron bivalent, oral	643 (46.5)	640 (46.5)
Ferrous sodium citrate	12 (0.9)	9 (0.7)
Iron in other combinations	140 (10.1)	171 (12.4)
Iron in combination with folic acid	121 (8.7)	120 (8.7)
Iron trivalent, oral	97 (7.0)	91 (6.6)
Ferric citrate	6 (0.4)	1 (<0.1)
Iron preparations	15 (1.1)	15 (1.1)
Anti-anemia preparations	2 (0.1)	8 (0.6)
Iron, parenteral	3 (0.2)	0
Other	1 (<0.1)	0
Dihydropyridine derivatives	865 (62.5)	879 (63.8)
Statins	711 (51.4)	703 (51.1)
Angiotensin II antagonists	588 (42.5)	571 (41.5)
Proton pump inhibitors	585 (42.3)	479 (34.8)
Platelet aggregation inhibitors[a]	578 (41.8)	527 (38.3)
Vitamin D and analogs	482 (34.8)	429 (31.2)
Beta blocking agents, selective	470 (34.0)	460 (33.4)
Phosphate binders	396 (28.6)	310 (22.5)
Angiotensin converting enzyme inhibitors	329 (23.8)	273 (19.8)
Insulin and analogs for injection, fast acting	313 (22.6)	246 (17.9)
Alpha and beta blocking agents	300 (21.7)	250 (18.2)
Insulin and analogs for injection, long acting	274 (19.8)	229 (16.6)
Other anti-parathyroid agents	52 (3.8)	38 (2.8)

[a]Excluding heparin.

Includes allowed medications that began prior to and were ongoing after randomization, or that began between the day of randomization and the day prior to last dose of study drug.

Supplemental Table 4. Exposure by dose

Dose/week	Dose, mg	Roxadustat (*n*=1384)	Placebo (*n*=1376)
		Patients ever receiving, *n* (%)	Patients ever receiving, *n* (%)
1	20	180 (13.0)	28 (2.0)
2	20	328 (23.7)	36 (2.6)
3	20	563 (40.7)	57 (4.1)
3	40	759 (54.8)	79 (5.7)
3	50	1003 (72.5)	178 (12.9)
3	70	1383 (99.9)	1374 (99.9)
3	100	834 (60.3)	1256 (91.3)
3	150	469 (33.9)	1068 (77.6)
3	200	188 (13.6)	594 (43.2)
3	250	57 (4.1)	222 (16.1)
3	300	16 (1.2)	69 (5.0)

OT+28 analysis set. Percentages were based on the number of patients in the OT+28 analysis set in that treatment arm.

OT, on-treatment.

Supplemental Table 5. Proportions of patients with at least one dose reduction or increase during treatment

	Roxadustat (*n*=1384)	Placebo (*n*=1376)
≥1 dose reduction	1204 (87.0)	577 (41.9)
≥1 dose increase	1242 (89.7)	1247 (90.6)

OT+28 analysis set. Data shown are number and percentage of patients. Percentages were based on the number of patients in the OT+28 analysis set in that treatment arm. During treatment refers to from randomization until the last dose of study drug.

OT, on-treatment.

Supplemental Table 6. Secondary efficacy end points

End point	Roxadustat (*n*=1384)		Placebo (*n*=1377)		Difference in LSM changes (95% CI)[a]	*P* value
	n	Rate of change estimate (95% CI) / Adjusted LSM (SE)[a]	*n*	Rate of change estimate (95% CI) / Adjusted LSM (SE)[a]		
8. Change from baseline in SF-36 Vitality sub-score over weeks 12 to 28	1279	1.59 (0.23)	1235	1.15 (0.23)	0.44 (–0.11, 0.99)	0.120[b]
9. Rate of change in eGFR from baseline during entire treatment period, mL/min/1.73 m^2	1326	–3.70 (–4.04, –3.35)	1314	–3.19 (–3.55, –2.83)	–0.51 (–1.00, –0.01)	Nominal *P*=0.046
10. Change from baseline in SF-36 Physical Functioning sub-score over weeks 12 to 28	1279	0.14 (0.22)	1234	–0.39 (0.22)	0.52 (0.0, 1.05)	Nominal *P*=0.051

[a]Rate of change estimate (95% CI) and rate of change difference (95% CI) are presented for secondary end point 9; adjusted LSM change (SE) and difference in LSM changes (95% CI) are presented for secondary endpoints 8 and 10.

[b]The difference was not statistically significant; therefore, the formal statistical hypothesis testing was stopped, and no further statistical testing was performed for all subsequent secondary end points.

CI, confidence interval; eGFR, estimated glomerular filtration rate; LSM, least-squares mean; SE, standard error; SF, short-form.

Supplemental Table 7. Most common serious adverse events (≥1%) by system organ class and preferred term (ITT analysis set)[a]

Preferred term	Roxadustat (*n*=1384)			Placebo (*n*=1377)		
	Patients with event	%	Event rate (per 100 P-Y)[b]	Patients with event	%	Event rate (per 100 P-Y)[b]
Infections and infestations						
Pneumonia	113	8.2	4.14	88	6.4	3.29
Sepsis	49	3.5	1.75	23	1.7	0.84
Urinary tract infection	36	2.6	1.29	26	1.9	0.96
Cellulitis	24	1.7	0.86	13	0.9	0.48
Septic shock	18	1.3	0.64	15	1.1	0.55
Peritonitis	15	1.1	0.53	14	1.0	0.51
Device-related infection	14	1.0	0.50	5	0.4	0.18
Metabolism and nutrition disorders						
Hyperkalemia	41	3.0	1.48	25	1.8	0.92
Hypoglycemia	32	2.3	1.14	26	1.9	0.96
Fluid overload	20	1.4	0.71	22	1.6	0.81
Hyperglycemia	16	1.2	0.57	9	0.7	0.33
Nervous system disorders						
Cerebrovascular accident	15	1.1	0.53	11	0.8	0.40
Cardiac disorders						
Cardiac failure congestive	33	2.4	1.18	31	2.3	1.14
Acute myocardial infarction	26	1.9	0.92	27	2.0	0.99
Cardiac failure	25	1.8	0.89	32	2.3	1.18
Myocardial infarction	14	1.0	0.50	13	0.9	0.47
Cardiac failure acute	8	0.6	0.28	14	1.0	0.51
Vascular disorders						

Hypertensive crisis	33	2.4	1.18	27	2.0	0.99
Hypertensive emergency	21	1.5	0.75	21	1.5	0.77
Hypertension	17	1.2	0.61	16	1.2	0.59
Deep vein thrombosis	15	1.1	0.53	4	0.3	0.15
Respiratory, thoracic, and mediastinal disorders						
Pulmonary edema	17	1.2	0.60	16	1.2	0.59
Pleural effusion	15	1.1	0.53	16	1.2	0.59
Acute pulmonary edema	13	0.9	0.46	22	1.6	0.81
Acute respiratory failure	12	0.9	0.43	20	1.5	0.73
Gastrointestinal disorders						
Gastrointestinal hemorrhage	20	1.4	0.71	15	1.1	0.55
Gastritis	18	1.3	0.64	15	1.1	0.55
Renal and urinary disorders						
End stage renal disease	199	14.4	7.68	201	14.6	8.06
Azotemia	61	4.4	2.20	60	4.4	2.24
Acute kidney injury	41	3.0	1.47	32	2.3	1.18
General disorders and administration site conditions						
Death	43	3.1	1.52	28	2.0	1.02
Generalized edema	17	1.2	0.61	7	0.5	0.26
Injury, poisoning, and procedural complications						
Arteriovenous fistula thrombosis	18	1.3	0.64	9	0.7	0.33

[a]Included SAEs with an onset date on or after the date of randomization and up to and including the end of study visit, withdrawal of consent, or date of last contact.

[b]Calculated as [Number of patients with SAEs divided by (the total number of days at risk for that SAE across all patients in given group divided by 365.25)] × 100.

Included AEs that were assessed to be serious by the Investigator, or where this assessment was missing. Percentages were based on the number of patients in the ITT analysis set in that treatment arm.

AE, adverse event; ITT, intent-to-treat; P-Y, patient-years; SAE, serious AE.

Supplemental Table 8. Serious adverse events within the cardiac disorders system organ class, by preferred term (ITT analysis set)[a]

Preferred term	Roxadustat (*n*=1384)			Placebo (*n*=1377)		
	Patients with event	%	Event rate (per 100 P-Y)[b]	Patients with event	%	Event rate (per 100 P-Y)[b]
Cardiac failure congestive	33	2.4	1.18	31	2.3	1.14
Acute myocardial infarction	26	1.9	0.92	27	2.0	0.99
Cardiac failure	25	1.8	0.89	32	2.3	1.18
Myocardial infarction	14	1.0	0.50	13	0.9	0.47
Coronary artery disease	12	0.9	0.43	7	0.5	0.26
Angina pectoris	10	0.7	0.36	9	0.7	0.33
Angina unstable	10	0.7	0.36	10	0.7	0.37
Atrial fibrillation	10	0.7	0.35	12	0.9	0.44
Cardiac arrest	9	0.7	0.32	4	0.3	0.15
Acute coronary syndrome	8	0.6	0.28	5	0.4	0.18
Cardiac failure acute	8	0.6	0.28	14	1.0	0.51
Arrhythmia	6	0.4	0.21	3	0.2	0.11
Cardio-respiratory arrest	6	0.4	0.21	4	0.3	0.15
Acute left ventricular failure	5	0.4	0.18	4	0.3	0.15
Cardiac failure chronic	4	0.3	0.14	5	0.4	0.18
Myocardial ischemia	4	0.3	0.14	8	0.6	0.29
Cardiac asthma	3	0.2	0.11	0	0	0
Cardiogenic shock	3	0.2	0.11	1	<0.1	0.04
Cardiopulmonary failure	3	0.2	0.11	1	<0.1	0.04
Pericardial effusion	3	0.2	0.11	0	0	0
Bradycardia	2	0.1	0.07	3	0.2	0.11

Cardiomyopathy	2	0.1	0.07	1	<0.1	0.04
Congestive cardiomyopathy	2	0.1	0.07	0	0	0
Left ventricular failure	2	0.1	0.07	0	0	0
Sinus node dysfunction	2	0.1	0.07	0	0	0
Aortic valve stenosis	1	<0.1	0.04	0	0	0
Arteriosclerosis coronary artery	1	<0.1	0.04	1	<0.1	0.04
Atrial flutter	1	<0.1	0.04	0	0	0
Atrioventricular block	1	<0.1	0.04	0	0	0
Cardiomegaly	1	<0.1	0.04	0	0	0
Coronary artery insufficiency	1	<0.1	0.04	0	0	0
Heart valve incompetence	1	<0.1	0.04	0	0	0
Heart valve stenosis	1	<0.1	0.04	0	0	0
Hypertensive cardiomyopathy	1	<0.1	0.04	0	0	0
Left ventricular dysfunction	1	<0.1	0.04	1	<0.1	0.04
Mitral valve incompetence	1	<0.1	0.04	0	0	0
Pulseless electrical activity	1	<0.1	0.04	1	<0.1	0.04
Sinoatrial block	1	<0.1	0.04	0	0	0
Sinus bradycardia	1	<0.1	0.04	0	0	0
Supraventricular tachycardia	1	<0.1	0.04	1	<0.1	0.04
Ventricular extrasystoles	1	<0.1	0.04	0	0	0
Ventricular fibrillation	1	<0.1	0.04	3	0.2	0.11
Atrioventricular block complete	0	0	0	1	<0.1	0.04
Bradyarrhythmia	0	0	0	1	<0.1	0.04
Bundle branch block left	0	0	0	1	<0.1	0.04

Cardiac tamponade	0	0	0	1	<0.1	0.04
Chronic left ventricular failure	0	0	0	1	<0.1	0.04
Coronary artery stenosis	0	0	0	1	<0.1	0.04
Ischemic cardiomyopathy	0	0	0	1	<0.1	0.04
Left ventricular hypertrophy	0	0	0	1	<0.1	0.04
Metabolic cardiomyopathy	0	0	0	2	0.1	0.07
Mitral valve disease	0	0	0	1	<0.1	0.04
Right ventricular failure	0	0	0	2	0.1	0.07
Sinus arrest	0	0	0	1	<0.1	0.04
Tachycardia	0	0	0	2	0.1	0.07
Ventricular arrhythmia	0	0	0	1	<0.1	0.04
Ventricular tachycardia	0	0	0	2	0.1	0.07

[a]Included SAEs with an onset date on or after the date of randomization and up to and including the end of study visit, withdrawal of consent, or date of last contact.

[b]Calculated as [Number of patients with SAEs divided by (the total number of days at risk for that SAE across all patients in given group divided by 365.25)] × 100.

Percentages were based on the number of patients in the ITT analysis set in that treatment arm.

ITT, intent-to-treat; P-Y, patient-years; SAE, serious adverse event.

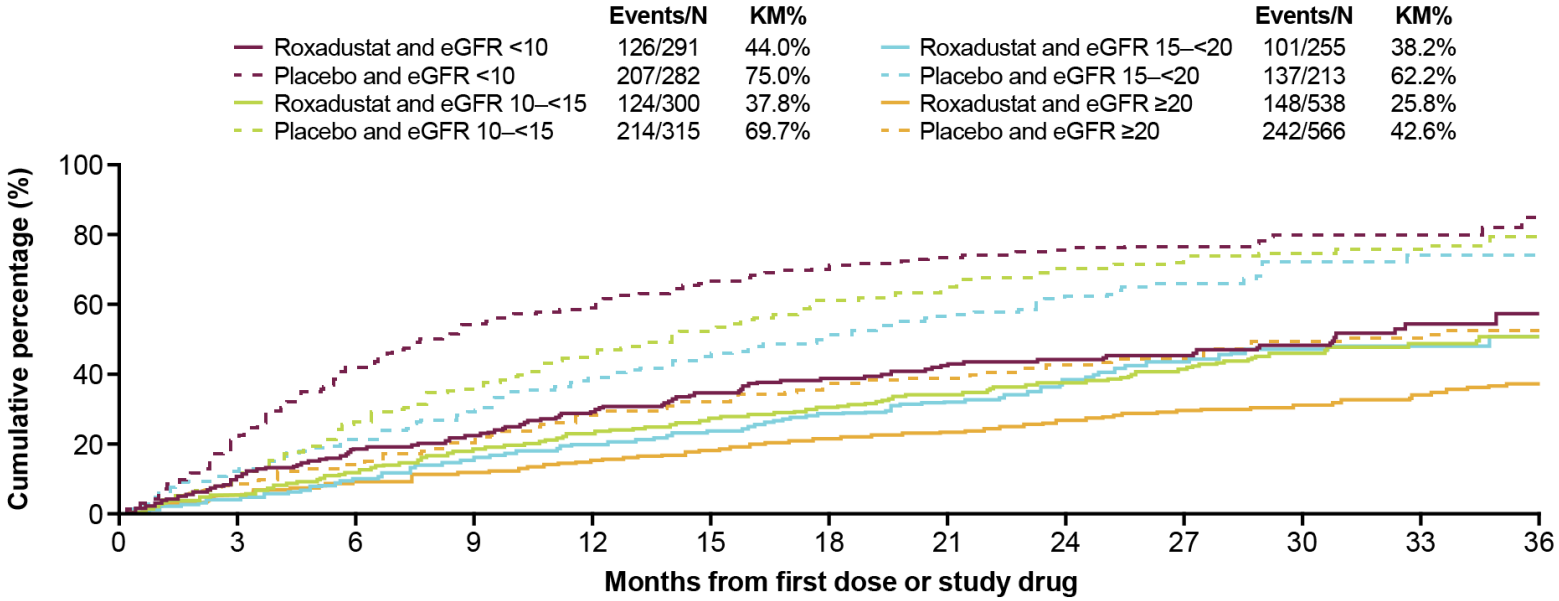
Supplemental Table 9. Serum potassium treatment-emergent laboratory values (OT+28 analysis set)

Outcome	Roxadustat (*n*=1384)	Placebo (*n*=1376)
Serum potassium, mmol/L, mean (SD)		
Baseline	4.77 (0.690)	4.76 (0.690)
End of treatment	4.89 (0.769)	4.79 (0.712)
Change from baseline	0.05 (0.522)	0.01 (0.541)
Serum potassium, mmol/L, *n* (%)[a]		
≤3.5	218 (15.8)	204 (14.8)
≥6.0	350 (25.3)	259 (18.8)
≥6.5	143 (10.3)	94 (6.8)
≥7.0	54 (3.9)	34 (2.5)

[a]Patients are included in a category if they had at least one post-baseline value fulfilling the criteria. Data shown in the table exclude measurements taken after initiation of dialysis. Baseline is defined as the last measurement prior to randomization.

OT, on-treatment; SD, standard deviation.

Supplemental Figure 1. Time to premature study drug discontinuation by treatment arm and baseline eGFR (OT+28 analysis set)



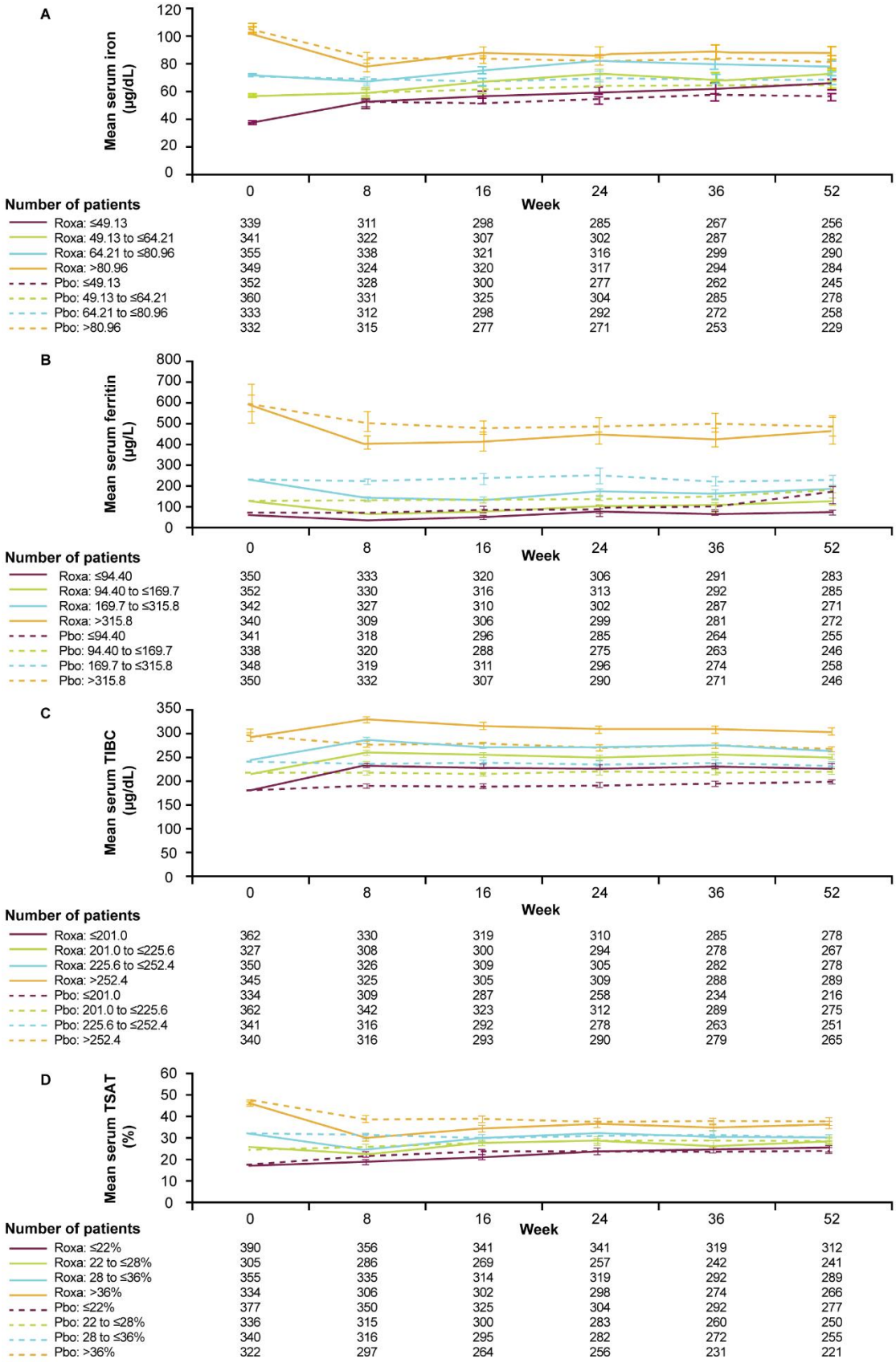
Number at risk

Roxadustat <10	291	253	219	202	181	162	141	120	90	66	47	27	13
Placebo <10	282	216	155	120	106	86	70	61	47	29	14	12	6
Roxadustat 10–<15	300	283	261	241	225	209	183	161	127	99	61	38	18
Placebo 10–<15	315	281	224	191	163	139	105	87	60	39	29	19	6
Roxadustat 15–<20	255	242	228	213	199	184	152	124	90	63	38	25	8
Placebo 15–<20	213	186	166	149	130	114	96	71	49	32	21	15	6
Roxadustat ≥20	538	502	477	456	433	397	354	294	234	172	120	79	31
Placebo ≥20	566	513	473	425	381	345	291	253	191	137	93	53	22

KM percentages were calculated at 24 months. Permanent discontinuation criteria: patient decision or investigator decision (adverse event, severe non-compliance, need for a third cycle of ESA rescue therapy, or initiation of dialysis and need for ESA rescue therapy).

eGFR, estimated glomerular filtration rate; ESA, erythropoiesis-stimulating agent; KM, Kaplan–Meier; N, number of patients in that treatment arm; OT, on-treatment.

Supplemental Figure 2. Serum iron parameters by visit, according to baseline quartile. A) Iron; B) Ferritin; C) TIBC; D) TSAT (ITT 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. ITT, intent-to-treat; Pbo, placebo; Roxa, roxadustat; TIBC, total iron binding capacity; TSAT, transferrin saturation.

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