Roxadustat for the Treatment of Anemia in Chronic Kidney Disease (CKD) Patients Not on Dialysis: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study (ALPS)

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Supplemental Material

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Supplemental Methods

Inclusion Criteria

Patients were eligible for the study if all of the following applied:

1. Institutional Review Board (IRB)-/Independent Ethics Committee (IEC)-approved written informed consent and privacy language as per national regulations were obtained from the patient or legally authorized representative prior to any study-related procedures (including extraction of prohibited medication, if applicable).
2. Patient age was ≥18 years.
3. Patient had a diagnosis of chronic kidney disease (CKD), with Kidney Disease Outcomes Quality Initiative Stage 3, 4, or 5, not receiving dialysis; with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, estimated using the abbreviated 4-variable Modification of Diet in Renal Disease (MDRD) equation.
4. The mean of the patient's three most recent haemoglobin (Hb) values during the screening period, obtained at least 4 days apart, was ≤10.0 g/dL, with a difference of ≤1.0 g/dL between the highest and the lowest values. The last Hb value was to be within 10 days prior to randomization.
5. Patient had a ferritin level ≥30 ng/mL (≥ 67.4 pmol/L) at screening.
6. Patient had a transferrin saturation (TSAT) level ≥5% at screening.
7. Patient had a serum folate level ≥ lower limit of normal at screening.
8. Patient had a serum vitamin B12 level ≥ lower limit of normal at screening.
9. Patient's alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were ≤3 x upper limit of normal (ULN), and total bilirubin (TBL) is ≤ 1.5 x ULN.
10. Patient's body weight was at least 45.0 kg, up to a maximum of 160.0 kg.
11. Female patients were either:
    - Of non-childbearing potential:
        i. postmenopausal (defined as at least 1 year without any menses) prior to screening, or
        ii. documented surgically sterile
    - Or if of childbearing potential:
        i. agreed not to try to become pregnant during the study and for 28 days after the final study drug administration
        ii. must have a negative serum pregnancy test at screening
        iii. if heterosexually active, agree to consistently use a highly effective form of birth control* starting at screening and throughout the study period, and continued for 28 days after the last study treatment administration
12. Male patients and their female spouse/partner(s) who were of childbearing potential must be using highly effective contraception starting at screening and continuing throughout the study period, and for 12 weeks after final study treatment administration.
    - Highly effective forms of birth control included:
        i. Consistent and correct usage of established oral contraception
        ii. Injected or implanted hormonal methods of contraception
        iii. Established intrauterine device (IUD) or intrauterine system (IUS)
        iv. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository (if allowed by local regulations)
        v. Any male partner that had undergone effective surgical sterilization
        vi. Any female partner that had undergone effective surgical sterilization, if applicable
13. Patient agreed not to participate in another interventional study from the time of signing informed consent until the end of study (EOS).

Exclusion Criteria

Patients were excluded from participation if any of the following applied:

1. Patient had received any erythropoiesis-stimulating agent (ESA) treatment within 12 weeks prior to randomization.
2. Patient had had more than one dose of intravenous (IV) iron within 12 weeks prior to randomization.
3. Patient had received a red blood cell (RBC) transfusion within 8 weeks prior to randomization.
4. Patient had a known history of myelodysplastic syndrome or multiple myeloma.

5. Patient had a known hereditary hematologic disease such as thalassemia or sickle cell anemia, pure red cell aplasia, or other known causes for anemia other than CKD.
6. Patient had a known hemosiderosis, hemochromatosis, coagulation disorder, or hypercoagulable condition.
7. Patient had chronic inflammatory disease that could impact erythropoiesis (eg, systemic lupus erythematosus, rheumatoid arthritis, celiac disease) even if it was currently in remission.
8. Patient was anticipated to have elective surgery that was expected to lead to significant blood loss or anticipated elective coronary revascularization.
9. Patient had active or chronic gastrointestinal bleeding.
10. Patient had received any prior treatment with roxadustat or a hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI).
11. Patient had been treated with iron-chelating agents within 4 weeks prior to randomization.
12. Patient had a history of chronic liver disease (eg, cirrhosis or fibrosis of the liver).
13. Patient had a known New York Heart Association Class III or IV congestive heart failure.
14. Patient had had a myocardial infarction, acute coronary syndrome, stroke, seizure, or a thrombotic/thromboembolic event (eg, pulmonary embolism) within 12 weeks prior to randomization.
15. Uncontrolled hypertension in the opinion of the investigator or two or more blood pressure (BP) values of systolic BP (SBP) ≥160 mmHg or diastolic BP (DBP) ≥95 mmHg confirmed by repeat measurement within 2 weeks prior to randomization. It should be noted that prior to version 2.0 of the protocol incorporating substantial amendment 1, the SBP threshold was ≥150 mmHg.
16. Patient had a diagnosis or suspicion (eg, complex kidney cyst of Bosniak Category 2F or higher) of renal cell carcinoma on renal ultrasound within 12 weeks prior to randomization.
17. Patient had a history of 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.
18. Patient was positive for any of the following: human immunodeficiency virus (HIV); hepatitis B surface antigen; or hepatitis C virus antibody.
19. Patient had an active clinically significant infection manifested by white blood count (WBC) > ULN, and/or fever, in conjunction with clinical signs or symptoms of infection within 1 week prior to randomization.
20. Patient had a known untreated proliferative diabetic retinopathy, diabetic macular edema, macular degeneration, or retinal vein occlusion.
21. Patient had had any prior organ transplant (that has not been explanted) or a scheduled organ transplantation.
22. Patient had participated in any interventional clinical study or had been treated with any investigational drugs within 30 days or 5 half-lives or limit set by national law, whichever was longer, prior to the initiation of screening.
23. Patient had an anticipated use of dapsone in any dose amount or chronic use of acetaminophen (paracetamol) >2.0 g/day during the treatment or follow-up period of the study.
24. Patient had a history of alcohol or drug abuse within 2 years prior to randomization.
25. Female patients:
    a. Must agree not to breastfeed starting at screening or during the study period, and continue for 28 days after the final study treatment administration
    b. Must not donate ova starting at screening and throughout the study period and continue for 28 days after final study drug administration
26. Male patients must not donate sperm starting at screening and throughout the study period and for 12 weeks after final study drug administration.
27. Any medical condition that in the opinion of the investigator posed a safety risk to a patient in this study, which may confound efficacy or safety assessment, or may interfere with study participation.

Protocol Revisions
The original study protocol (December 2012) was revised (December 2014). Patients who entered under the initial study protocol, upon signing the updated informed consent, adapted their dose frequency during the maintenance period and dose amount according to the instructions outlined in the revised protocol. Specifically, these changes included (a) dosing frequency during the maintenance period was changed from three times weekly (TIW), twice weekly (BIW), and once weekly (QW) to TIW only; (b) initial study drug dose was changed from 70, 100, and 150 mg to 70 and 100 mg only; (c) maximum dose was reduced from 3.5 mg/kg to 3.0 mg/kg; and (d) maximum absolute dose was reduced from 400 mg to 300 mg.

Treatment Compliance
The quantity of study drug dispensed to and returned by the patient was counted and recorded. If the patient was not compliant with study drug intake, the investigator discussed this with the patient. Deviations from the prescribed dose were recorded and required notification to the sponsor for assessment for recording as a protocol deviation.

Health-Related Quality of Life
All study patients were required to complete quality of life (QoL) questionnaires: Short Form-36 Health Survey (SF-36), Functional Assessment of Cancer Therapy-Anemia (FACT-An), EuroQol Questionnaire – 5-Dimensions 5-Levels (EQ-5D-5L), Patients' Global Impressions of Change (PGIC) Scale and Work Productivity and Activity Impairment questionnaire Anemic Symptoms (WPAI:AnS).

Short Form-36 Health Survey (SF-36) v2
The SF-36v2 is a QoL instrument designed to assess generic health concepts relevant across age, disease, and treatment groups. It is aimed at both adults and adolescents aged 18 years and older. The SF-36 consists of eight domains of health status: physical functioning (10 items), role physical (four items), bodily pain (two items), general health (five items), vitality (four items), social functioning (two items), role emotional (three items) and mental health (five items). Two component scores, the Physical Component Summary and the Mental Component Summary, can also be calculated. For both the SF-36 domain scores and summary scores, higher scores indicate better health status, with scores ranging from 0-100. United States (US)-normalized values were used for the analysis where the scores normed to the US population to have a mean of 50 and standard deviation of 10. The SF-36 has a recall period of the 'past 4 weeks.'

Functional Assessment of Cancer Therapy –Anemia (FACT-An)
The Functional Assessment of Cancer Therapy – General (FACT-G) Version 4 contains 27 items that cover four dimensions of well-being: physical (PWB)—seven items, functional well-being (FWB)—seven items, social/family (SWB)—seven items each, and emotional well-being (EWB)—six items. A subscale of 13 fatigue specific items (the Fatigue Subscale), plus seven additional items related to anemia, were developed for use in conjunction with the FACT-G [1]. The 13 fatigue items plus the seven additional items related to anemia comprise the anemia subscale (AnS). Administration of the FACT-G plus the AnS is referred to as the FACT-An. The FACT-An has a recall period of the 'past 7 days.' Respondents are asked to provide responses (ie, 'Not at all,' 'A little bit,' 'Somewhat,' 'Quite a bit,' and 'Very much') to a list of statements which are either positively or negatively phrased. For all FACT-An scales, a higher score indicates better QoL, with scores ranging from 0-188.

EuroQol Questionnaire – 5-Dimensions 5-Levels (EQ-5D-5L)
The EQ-5D-5L is a self-reported questionnaire. The EQ-5D is being used as a measure of respondents' HRQoL and utility values. The EQ- 5D consists of the EQ-5D descriptive system and the EQ visual analog scale (VAS). The EQ-5D descriptive system comprises five dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has five levels: no problems, slight problems, moderate problems, severe problems, extreme problems. The VAS records the respondent's self-rated health status on a graduated (0-100) scale, where the endpoints are labeled 'Worst imaginable health state' and 'Best imaginable health state' and with higher scores for higher HRQoL. EQ-5D health states, defined by the EQ-5D descriptive system, may be converted into a single summary index by applying a formula that essentially attaches values (also called weights) to each of the levels in each dimension. The index can be calculated by deducting the appropriate weights from 1, the value for full health (ie, state 11111).

Patients' Global Impression of Change (PGIC) Scale
The PGIC is a patient-rated instrument that measures change in patients' overall status on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse).

Work Productivity and Activity Impairment Questionnaire: Anemic Symptoms (WPAI:AnS)
The objective of the WPAI:AnS version 2 is to measure work and activity impairment during the past 7 days due to anemia. It is self-assessed. The two domains covered by the questionnaire are work and daily activities. The WPAI:AnS consists of six questions, including asking if the patient is working, how many hours the person missed work due to anemic symptoms, how many hours the patient actually worked, and how the anemic symptoms impacted the productivity and ability to do daily activities.

Rescue Therapy Guidelines
Rescue therapy guidelines were provided to optimize standardization of the use of rescue therapy by investigators and to ensure safety of the individual study patients. Use of rescue therapy and reason for rescue therapy was recorded in the electronic case report form. If patients met the criteria for ESA rescue therapy while on dialysis, ESAs were administered IV or SC according to the package insert or summary of product characteristics (SmPC) of the respective ESA for dialysis patients.

RBC Transfusion
In the event of acute or severe blood loss, RBC transfusion was allowed if clinically indicated. In a situation where there was no obvious blood loss, RBC transfusion was permitted if the patient had moderate to severe symptom(s) from their anemia (eg, dyspnea at rest or on mild exertion) and the investigator was of the opinion that the blood transfusion was a medical necessity. Study drug could be continued even if a blood transfusion had been administered.

ESA
If a patient's Hb level had not sufficiently responded to two or more dose increases or maximum dose (by body weight) of the study drug, and the investigator considered the initiation of an ESA (ie, EPO analog) rescue a medical necessity, the investigator was to consider initiating the use of an approved ESA only if all of the following criteria were met:

- The patient's Hb level had not sufficiently responded to two or more dose increases in the previous 8 weeks or maximum dose (by body weight) of the study drug
- The patient's Hb was <8.0 g/dL
- Reducing the risk of alloimmunization in transplant-eligible patients and/or reduction of other RBC transfusion-related risks was a goal

The patient could continue on study; however, the patient was not allowed to be administered both ESA and study drug during the same time period. The course of ESA (ie, the amount that could be administered) was limited by duration of therapy and effect on Hb, including that one course of ESA treatment would not exceed 4 weeks in duration, and that ESA rescue would be stopped as soon as Hb ≥9 g/dL. Treatment with study drug could be resumed as soon as possible after the following intervals:

- At least 2 days after stop of epoetin alfa or epoetin beta, or biosimilar thereof
- At least 1 week after stop of darbepoetin alfa
- At least 2 weeks after stop of methoxy polyethylene glycol-epoetin beta

If a patient required a third course of rescue with ESAs, the patient was to be discontinued. The patient was to complete the EOT visits (EOT visit and EOT + 2 weeks visit) and the EOS visit, and continue to be followed up with every 6 months for vital status and serious AEs, cardiovascular and thromboembolic AEs until their projected date of completion or, if earlier, until the last patient randomized reaches EOS. Instructions on ESA rescue treatments for patients moving from protocol v1.0 to protocol v2.0 were provided in protocol v2.0.

Intravenous Iron
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 route of treatment. The recommended daily oral dose was 200 mg of elemental iron. The investigator could initiate the use of IV iron supplement if:

- The patient's Hb level had not sufficiently responded to two or more dose increases of study drug while taking oral iron (unless not tolerated)
- Hb <8.5 g/dL and
- Ferritin <100 ng/mL, or TSAT <20%

If IV iron rescue criteria were met, the dose in a single administration (day) was to be no more than 250 mg. Study treatment could continue during IV iron administration. At 4 to 8 weeks after the single dose of IV iron, a repeat dose of IV iron could be administered if the Hb remained <9.0 g/dL and the patient still met iron deficiency criteria (ferritin <100 ng/mL or TSAT <20%). After this 8-week period, full IV iron rescue criteria would need to be met again in order to qualify a patient for a second course of IV iron at a later point in the study.

In Case of Hb Rate of Rise >2 g/dL Within 4 Weeks
If a blood transfusion or ESA had been performed within 2 weeks of meeting the criteria for Hb rate of rise >2 g/dL within 4 weeks, performing a dose reduction of the study drug for Hb rate of rise >2 g/dL within 4 weeks was not recommended.

Sample Size Calculations
This study was sufficiently powered for both regionally based primary efficacy endpoints. For the EU (EMA) primary efficacy endpoint, 300 patients for the roxadustat treatment group and 150 patients for the placebo treatment group were needed to achieve at least power of 95% to demonstrate a statistically significant difference with a 5% two-sided significance level between roxadustat and placebo in the primary endpoint, assuming that the proportion of patients with response in the roxadustat group is at least 65% and in the placebo group is at most 25%. For the USA (FDA) primary efficacy endpoint, a sample size of 450 would allow the study to have at least power of 99% to detect a 1.0-g/dL difference in mean Hb values between the two treatment groups, assuming that the common standard deviation was 1.2 g/dL using an analysis of variance (ANOVA) test with a 5% two-sided significance level.

Analysis Populations
Analysis populations included the all randomized set, which consisted of all randomized patients; the full analysis set (FAS), which consisted of all randomized patients who received at least one dose of study drug and had at least one non-missing post-dose Hb assessment; the per protocol set (PPS), which included all FAS patients who did not meet any of the criteria required to exclude a patient from the PPS; and the safety analysis set (SAF), which consisted of all randomized patients who received at least one dose of study drug.

Supplemental Results

Treatment Exposure

Overall treatment duration was longer in the roxadustat treatment group (median: 59.71 weeks) compared with the placebo treatment group (51.71 weeks), with a greater proportion of patients in the roxadustat treatment group receiving treatment for ≥52 weeks (61.3%) compared with the placebo treatment group (44.4%). Total patient exposure years (PEY) were 472.7 years in the roxadustat treatment group compared with 198.3 years in the placebo treatment group. In the safety-emergent period (defined as the evaluation period from the date of first drug intake up to 28 days after the last dose intake), median treatment duration and PEY were also longer in the roxadustat treatment group (63.71 weeks and 496.9 PEY) compared with the placebo group (55.71 weeks and 210.0 PEY); these imbalances are likely due to the 2:1 randomization ratio (roxadustat:placebo) and the greater number of patient discontinuations seen in the placebo treatment group. During the treatment period, average weekly consumed dose was lower in the roxadustat treatment group (251.0±134.5 mg) compared with the placebo treatment group (478.0±142.3 mg). Treatment compliance was comparable between roxadustat (100.4%) and placebo (100.3%) groups.

Secondary Efficacy Endpoints

There was no apparent difference between the roxadustat and placebo treatment groups in terms of change from baseline in mean arterial pressure (MAP) at each timepoint assessed. Specifically, the LSM change from baseline in MAP in Weeks 12-28 was -0.814 (95% CI: -1.83, 0.20) mmHg in the roxadustat treatment group and -1.656 (95% CI: -2.91, -0.41) mmHg in the placebo treatment group. The LSM difference for roxadustat versus placebo was 0.842 (95% CI: -0.40, 2.08; P=0.182).

Likewise, there was no apparent difference between the roxadustat and placebo treatment groups in terms of cumulative incidence of first occurrence of hypertension. Overall, 15.0% of patients in the roxadustat group and 10.9% of patients in the placebo group experienced an event of hypertension in the safety-emergent period. Cumulative time at risk was 402.0 years in the roxadustat treatment group and 166.0 years in the placebo treatment group; therefore, the incidence rate per 100 patient years at risk was 13.4 and 12.1, respectively, and the hazard ratio was 1.290 (95% CI: 0.77, 2.13; P=0.334).

There was no difference in decrease in eGFR with time, or between treatment groups. The LSM difference in estimated annualized eGFR slope for roxadustat versus placebo was 0.59 mL/min/1.73 m^2 per year (95% CI: -0.57, 1.75; P=0.316).

Change in Hb level from baseline to the average Hb of Weeks 28-36, Weeks 44-52, and Weeks 96-104 regardless of rescue therapy showed nominal superiority for roxadustat compared with placebo at each timepoint. The LSM difference (roxadustat – placebo) was 1.614 g/dL (95% CI: 1.42, 1.81; *P*<0.001) over Weeks 28-36, 1.594 g/dL (1.38, 1.81; *P*<0.001) over Weeks 44-52, and 1.452 g/dL (1.10, 1.80; *P*<0.001) over Weeks 96-104. Upon analyzing the time to first Hb response (as defined for the primary EU [EMA] endpoint) during the first 24 weeks without rescue therapy using Cox regression, roxadustat (544.5 events per 100 years at risk) demonstrated nominal superiority compared with placebo (29.7 events per 100 years at risk), with a hazard ratio of 19.001 (95% CI: 11.98, 30.15; *P*<0.001).

Cholesterol levels and apolipoproteins showed a decrease at each timepoint in the roxadustat treatment group compared with a slight increase in the placebo treatment group (**Supplemental Table 6**). A greater proportion of patients in the roxadustat treatment group (55.0%), compared with the placebo treatment group (49.8%) overall, were hospitalized; however, the mean number of hospitalizations per patient was comparable between treatment groups (2.1 vs 2.0 days) and the mean number of days of hospitalization PEY was lower in the roxadustat treatment group (26.5 days) compared with the placebo treatment group (31.9 days). There was no difference in the time to first hospitalization between the treatment groups (hazard ratio: 0.945 [95% CI: 0.74, 1.20; *P*=0.643]), with a comparable incidence rate of 68.4 events per 100 years at risk in the roxadustat treatment group compared with 73.9 in the placebo treatment group.

Changes in hepcidin and soluble transferrin receptor from baseline were greater in the roxadustat treatment group compared with the placebo treatment group at each visit (**Supplemental Figure 14**). At Week 52, mean (SD) hepcidin had decreased from 37.852 (36.633) µg/L in the roxadustat treatment group to 24.630 (30.136) µg/L, and from 41.163 (37.265) µg/L in the placebo group to 39.448 (37.827) µg/L. At Week 52, mean (SD) soluble transferrin receptor had increased from 47.66 (27.78) nmol/L to 64.61 (41.06) nmol/L in the roxadustat treatment group, and it changed slightly from 45.65 (22.94) nmol/L to 45.21 (23.26) nmol/L in the placebo group.

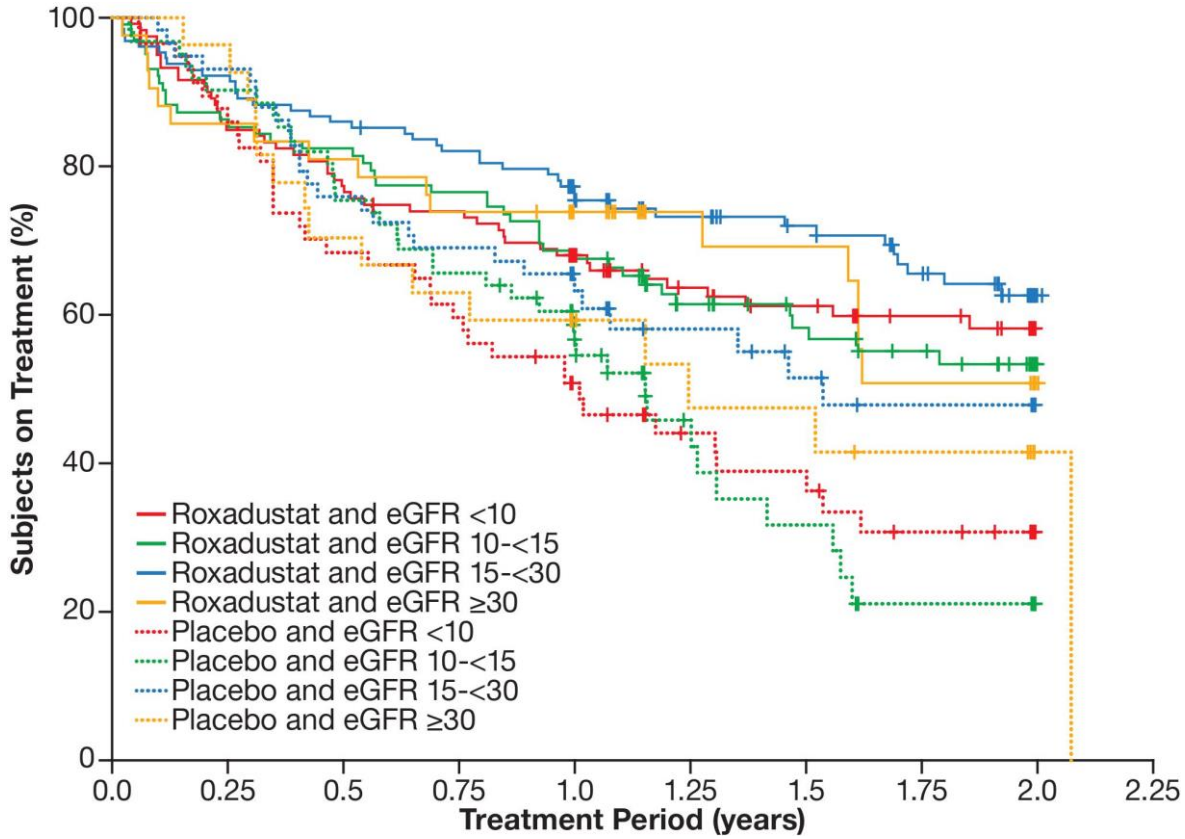
There were no apparent differences between treatment groups in any of the reported HRQoL scales.

Overall Deaths

Overall deaths, defined as all reported deaths after the first study drug administration, regardless of drug discontinuation, were 45 (11.5%) in roxadustat-treated patients and 20 (9.9%) in placebo-treated patients.

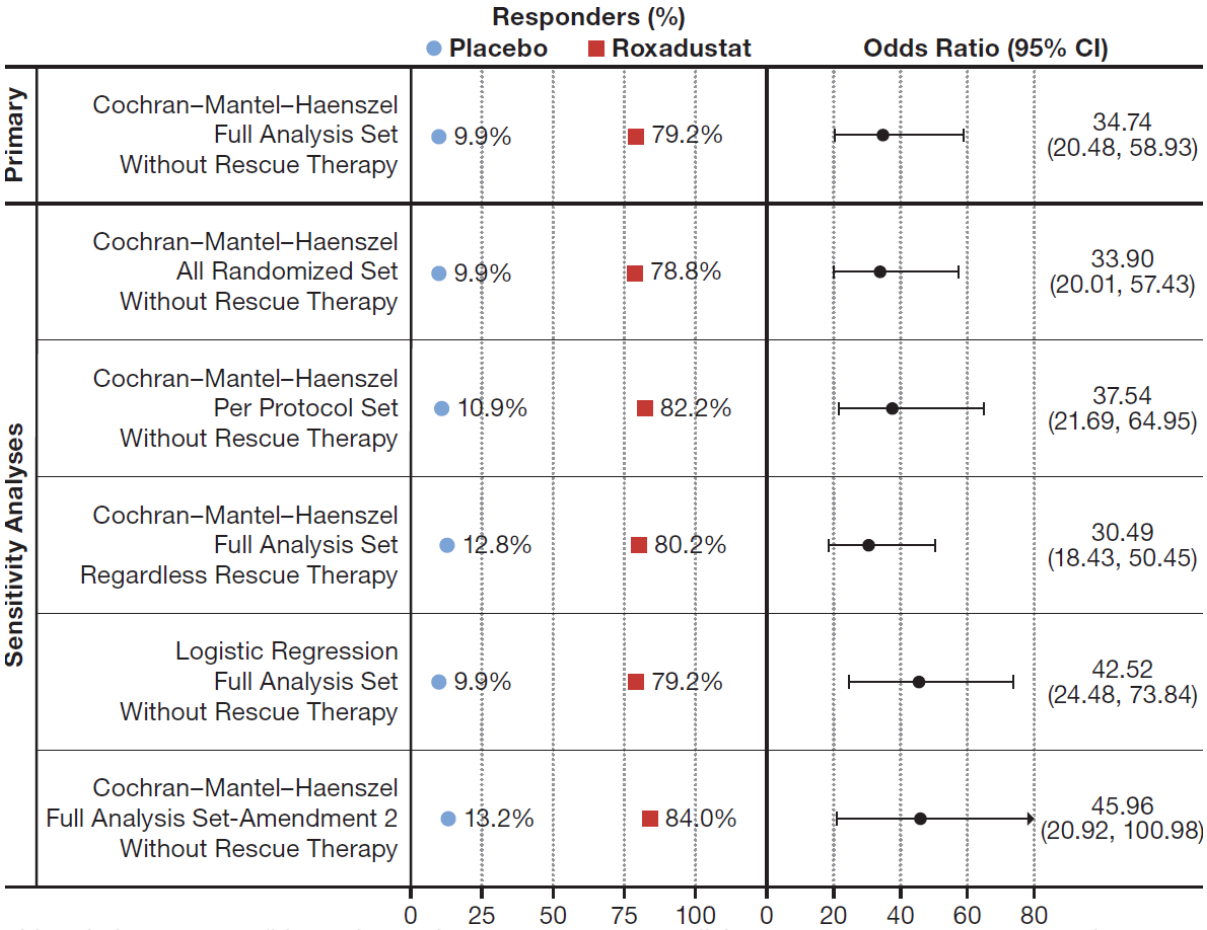
Supplemental Figures and Tables

Supplemental Figure 1. Treatment Discontinuation Rates by eGFR



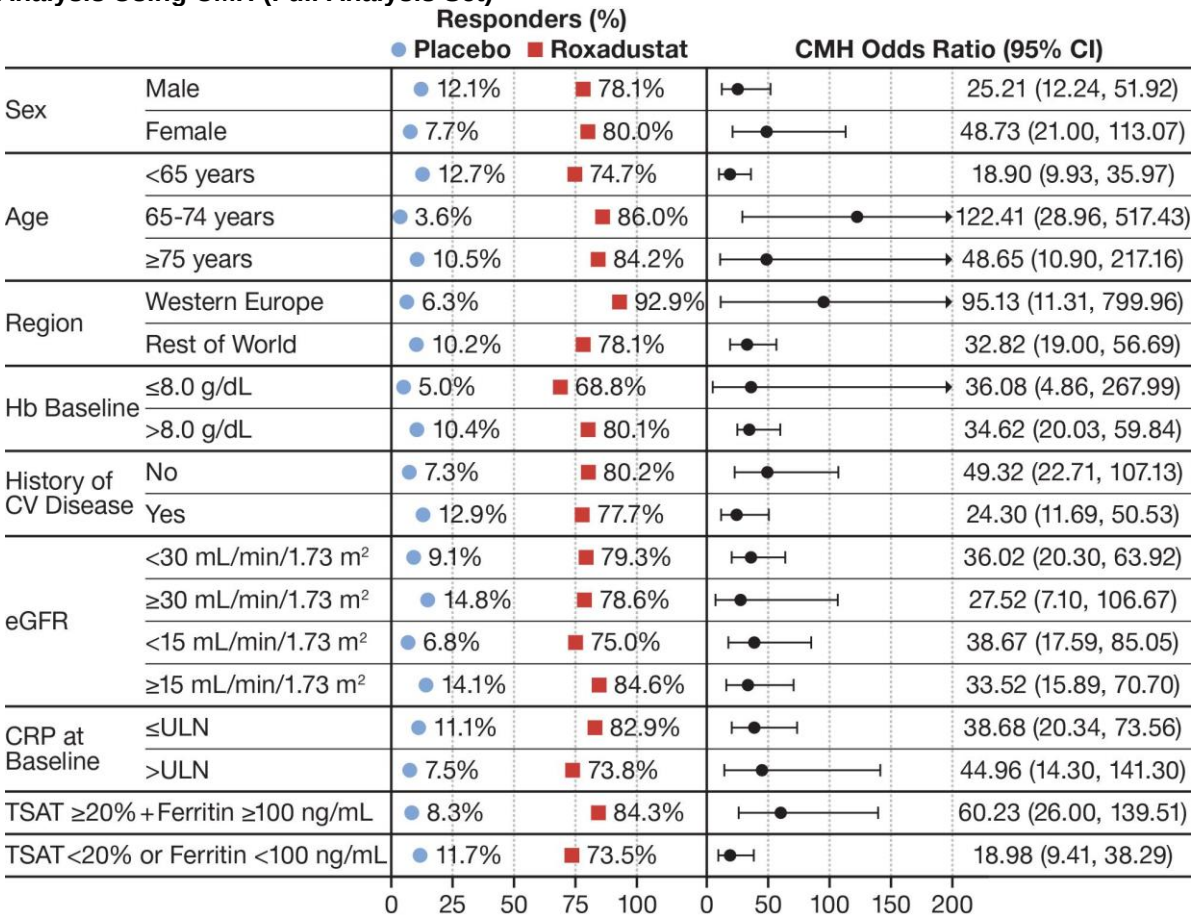
Abbreviation: eGFR, estimated glomerular filtration rate.

Supplemental Figure 2. Summary of Sensitivity Analyses of the Primary EU (EMA) Efficacy Analysis



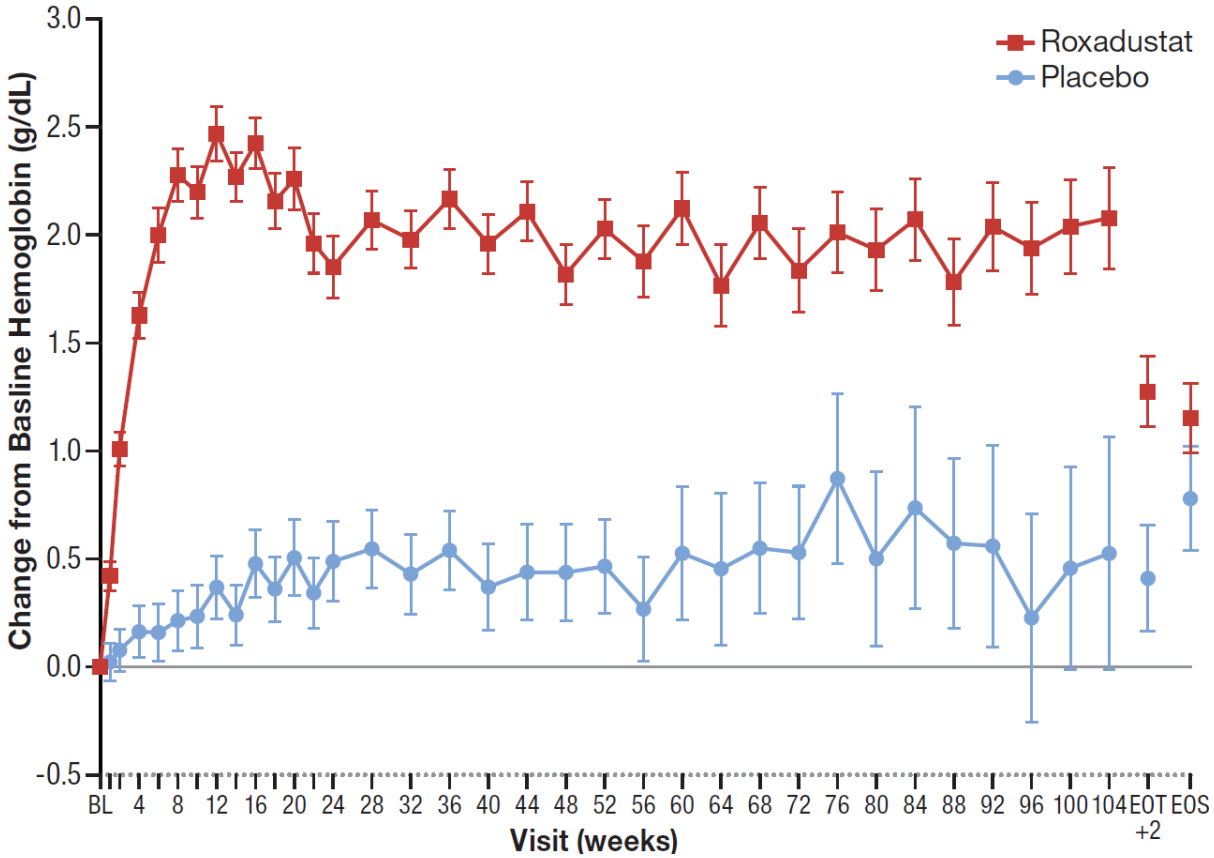
Abbreviations: CI, confidence interval; EMA, European Medicines Agency; EU, European Union; RT, rescue therapy.

Supplemental Figure 3. Summary of Subgroup Analyses of the Primary EU (EMA) Efficacy Analysis Using CMH (Full Analysis Set)



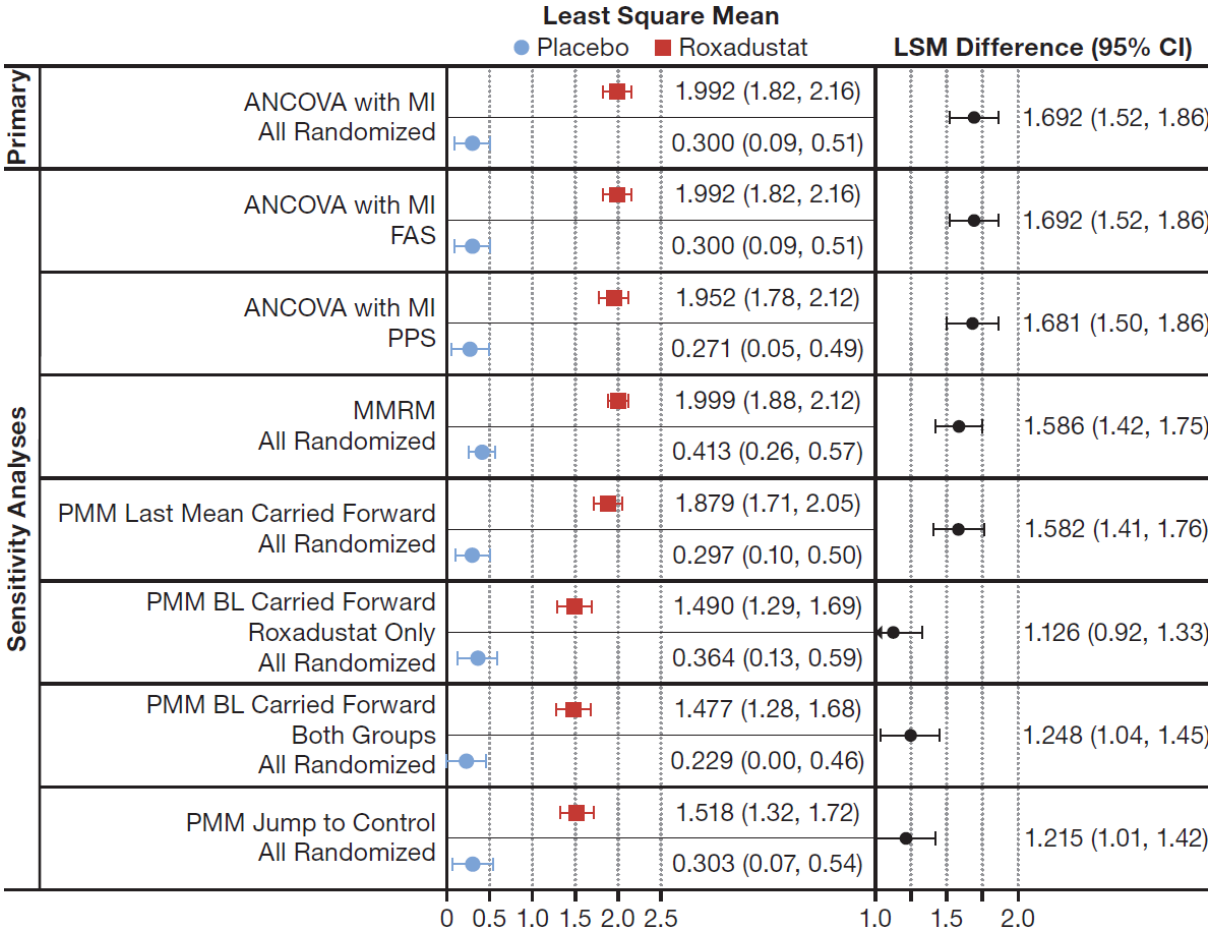
Abbreviations: CI, confidence interval; CMH, Cochran–Mantel–Haenszel; CRP, C-reactive protein; CV, cardiovascular; eGFR, estimated glomerular filtration rate; EMA, European Medicines Agency; EU, European Union; Hb, hemoglobin; TSAT, transferrin saturation; ULN, upper limit of normal.

Supplemental Figure 4. Mean Hb Change from Baseline Regardless of Rescue Therapy Use (All Randomized Patients)



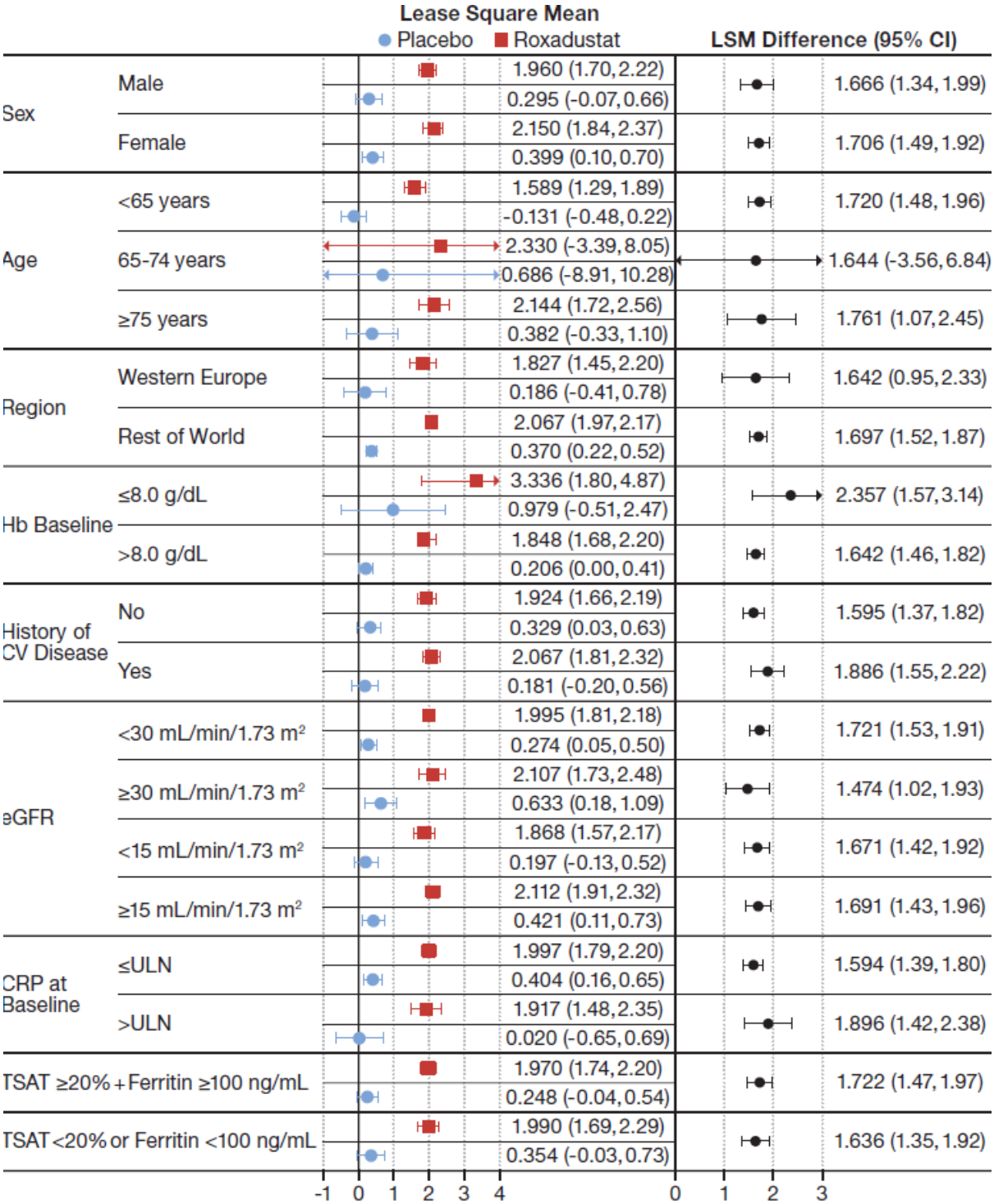
Abbreviations: EOS, end of study; EOT, end of treatment; Hb, hemoglobin.

Supplemental Figure 5. Summary of Sensitivity Analyses of the Primary US (FDA) Efficacy Analysis



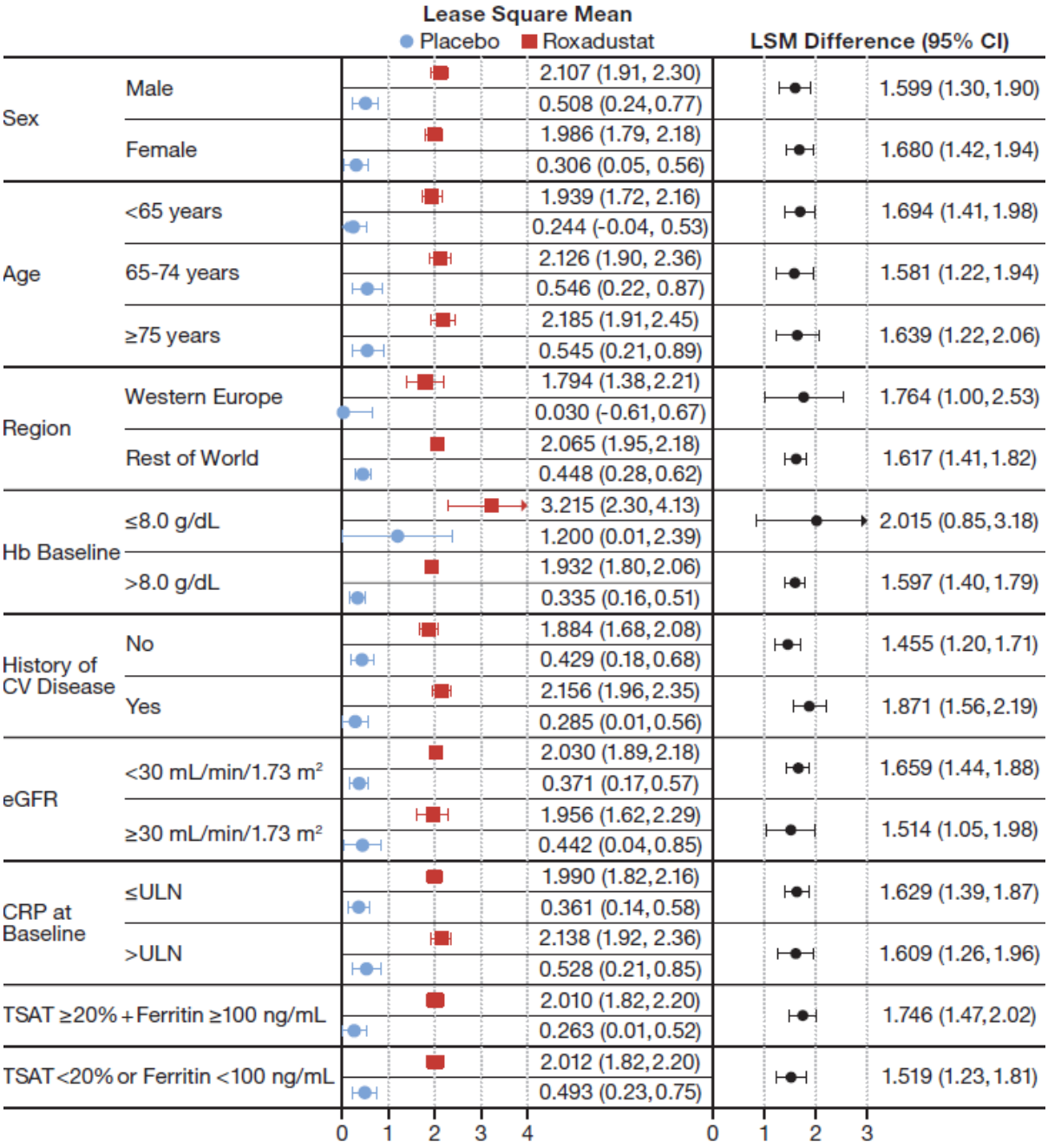
Abbreviations: ANCOVA, analysis of covariance; BL, baseline; CI, confidence interval; FAS, full analysis set; FDA, Food and Drug Administration; LSM, least square mean; MI, multiple imputations; PMM, pattern mixtures model; PPS, per protocol set; US, United States.
Unit for LSM and LSM difference is g/dL.

Supplemental Figure 6. Summary of Subgroup Analyses of the US (FDA) Primary Efficacy Endpoint (All Randomized Patients) Using ANCOVA with MI



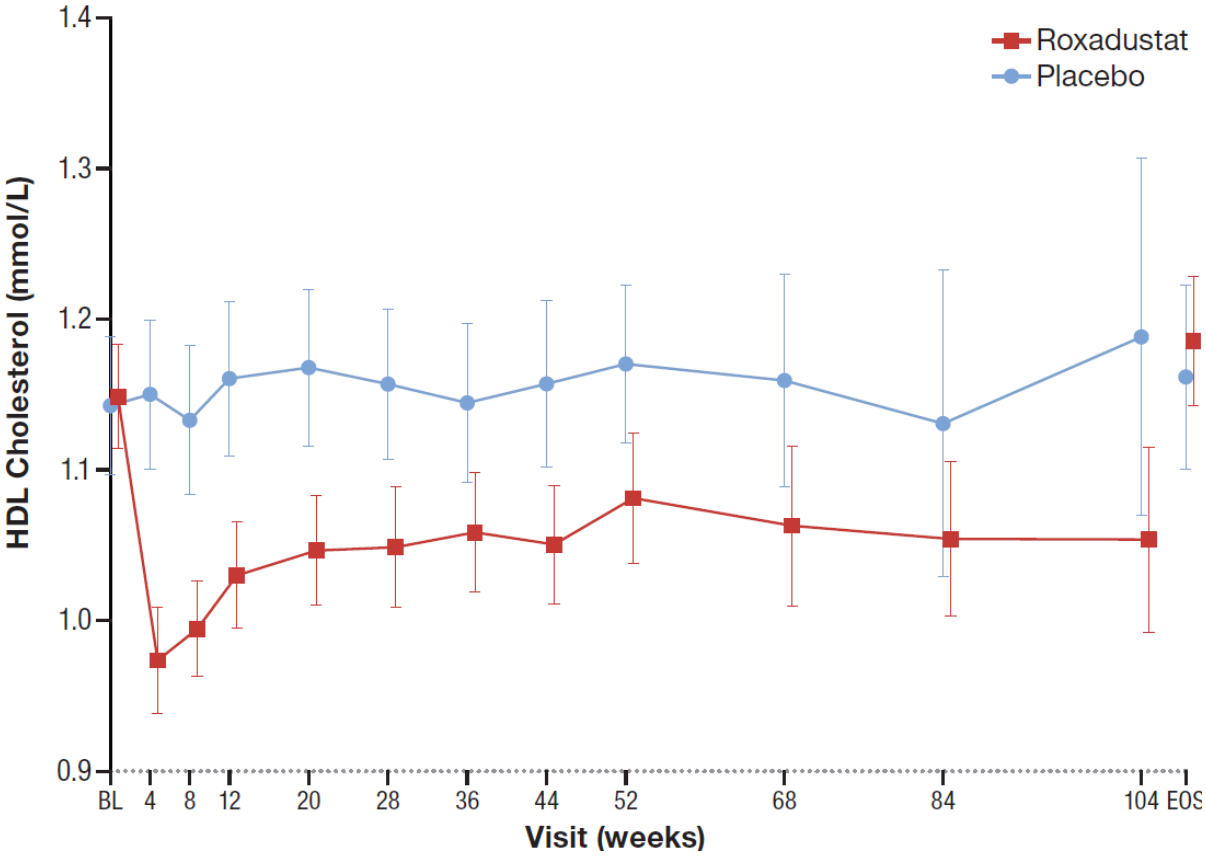
Abbreviations: ANCOVA, analysis of covariance; BL, baseline; CI, confidence interval; CRP, C-reactive protein; CV, cardiovascular; eGFR, estimated glomerular filtration rate; FDA, Food and Drug Administration; Hb, hemoglobin; LSM, least square mean; MI, multiple imputations; TSAT, transferrin saturation; ULN, upper limit of normal; US, United States.
Unit for LSM and LSM difference is g/dL.

Supplemental Figure 7. Subgroup Analysis of Change from Baseline to the Average Hb in Weeks 28-36 without Rescue Therapy, Full Analysis Set



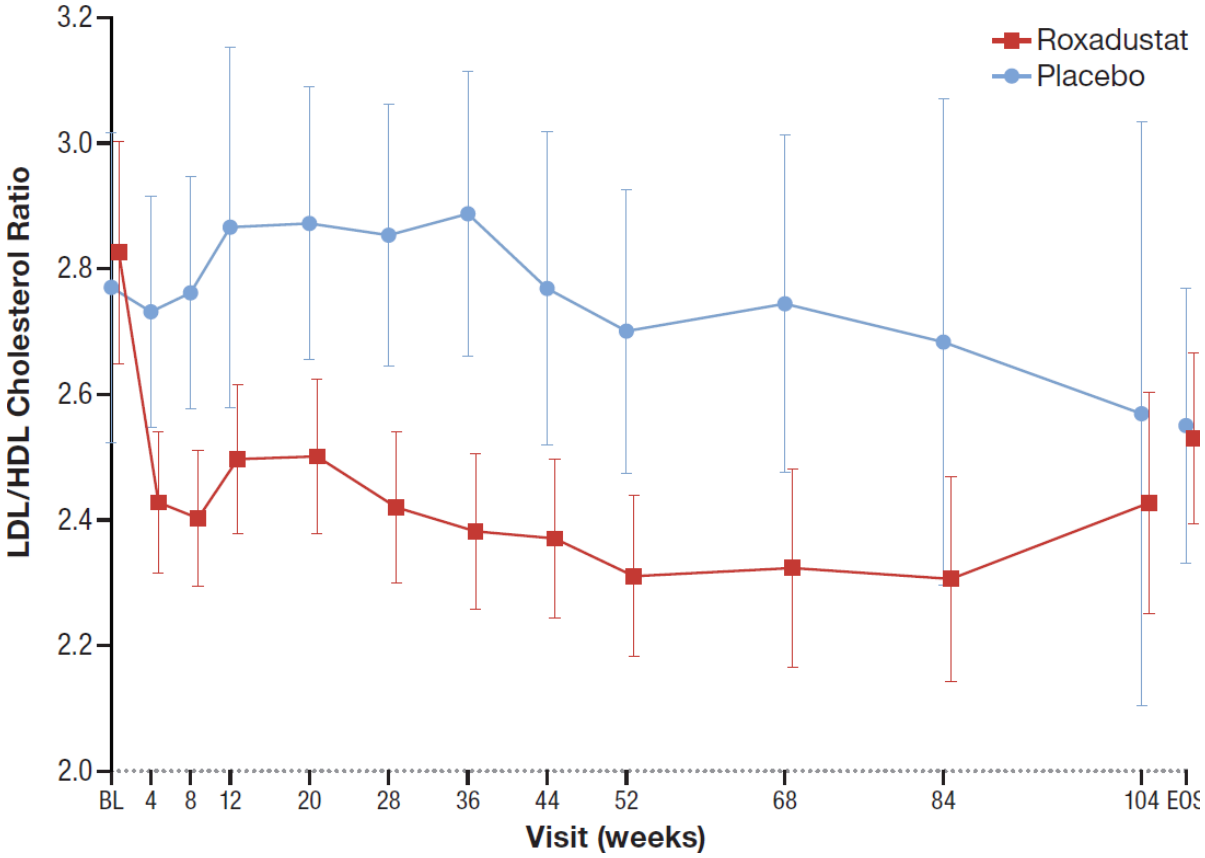
Abbreviations: CI, confidence interval; CRP, C-reactive protein; CV, cardiovascular; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; LSM, least square mean; TSAT, transferrin saturation; ULN, upper limit of normal; US, United States.
Unit for LSM and LSM difference is g/dL.

Supplemental Figure 8. Mean (± 95% CI) Plot of HDL Cholesterol (mmol/L), Safety Analysis Set



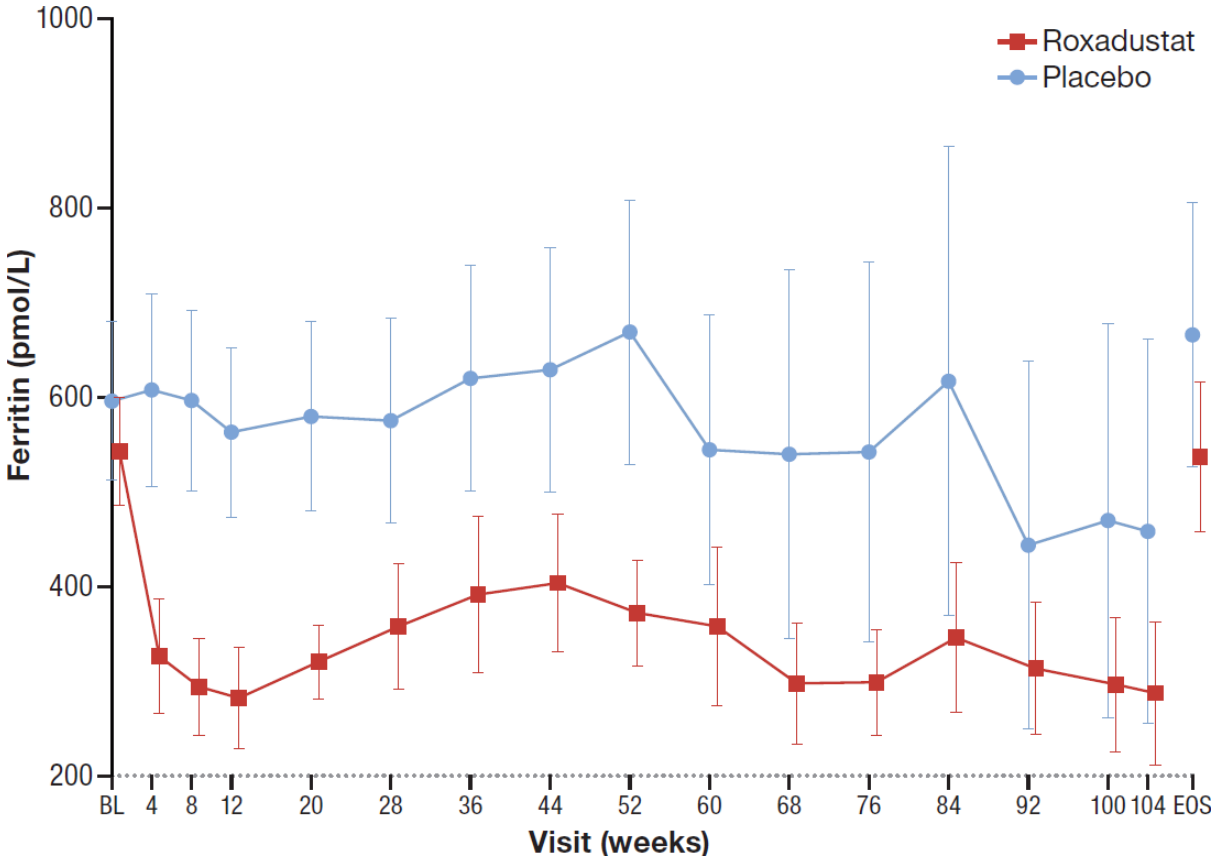
Abbreviations: CI, confidence interval; EOS, end of study; HDL, high-density lipoprotein.

Supplemental Figure 9. Mean (± 95% CI) Plot of LDL/HDL Cholesterol Ratio, Safety Analysis Set



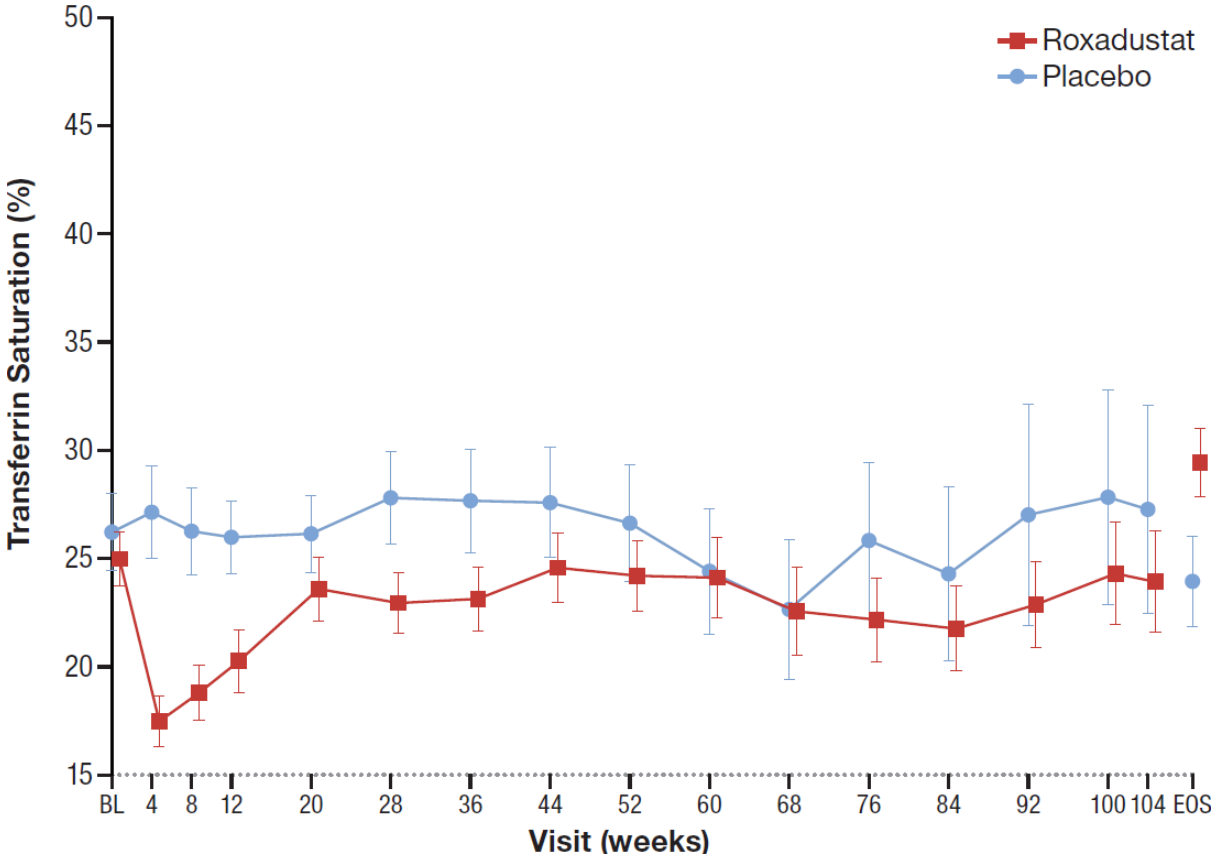
Abbreviations: CI, confidence interval; EOS, end of study; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Supplemental Figure 10. Mean (± 95% CI) Plot for Ferritin, Full Analysis Set



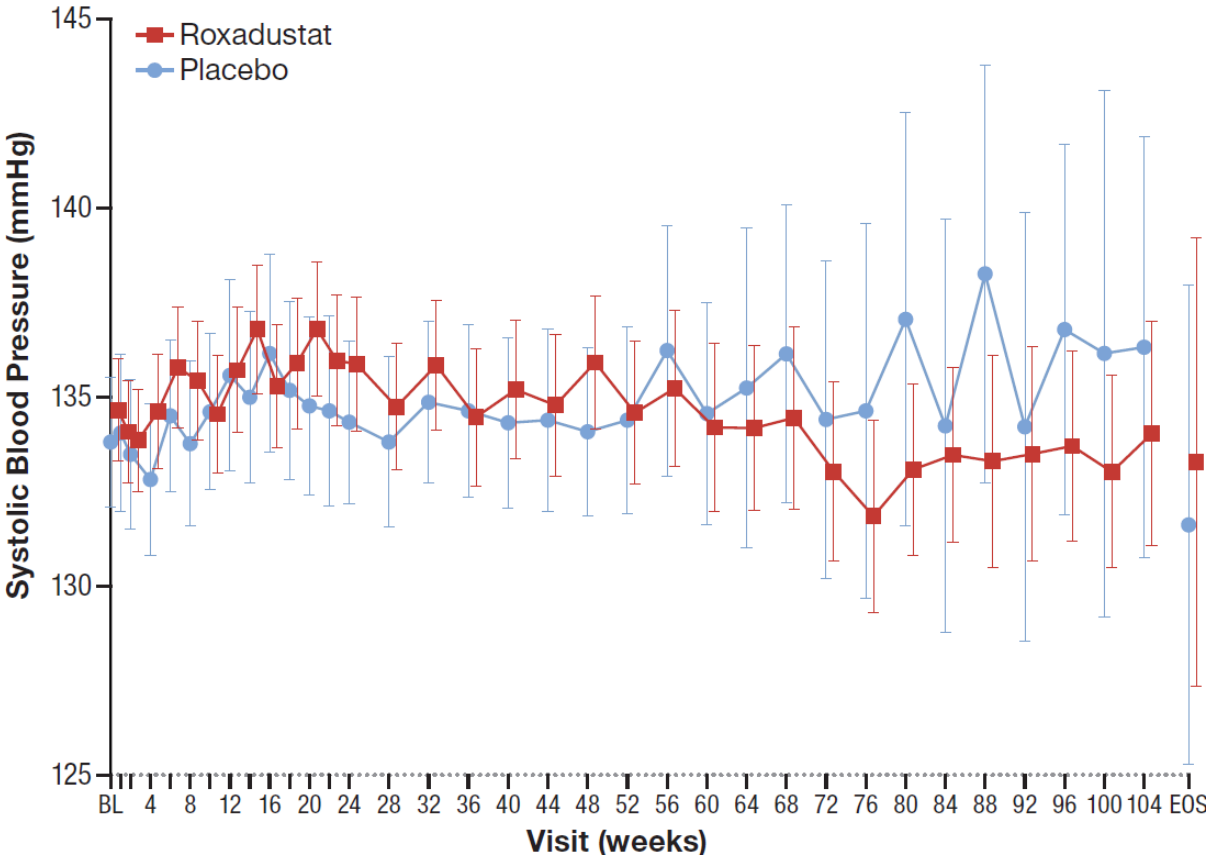
Abbreviation: CI, confidence interval; EOS, end of study.

Supplemental Figure 11. Mean (± 95% CI) Plot for Transferrin Saturation, Full Analysis Set



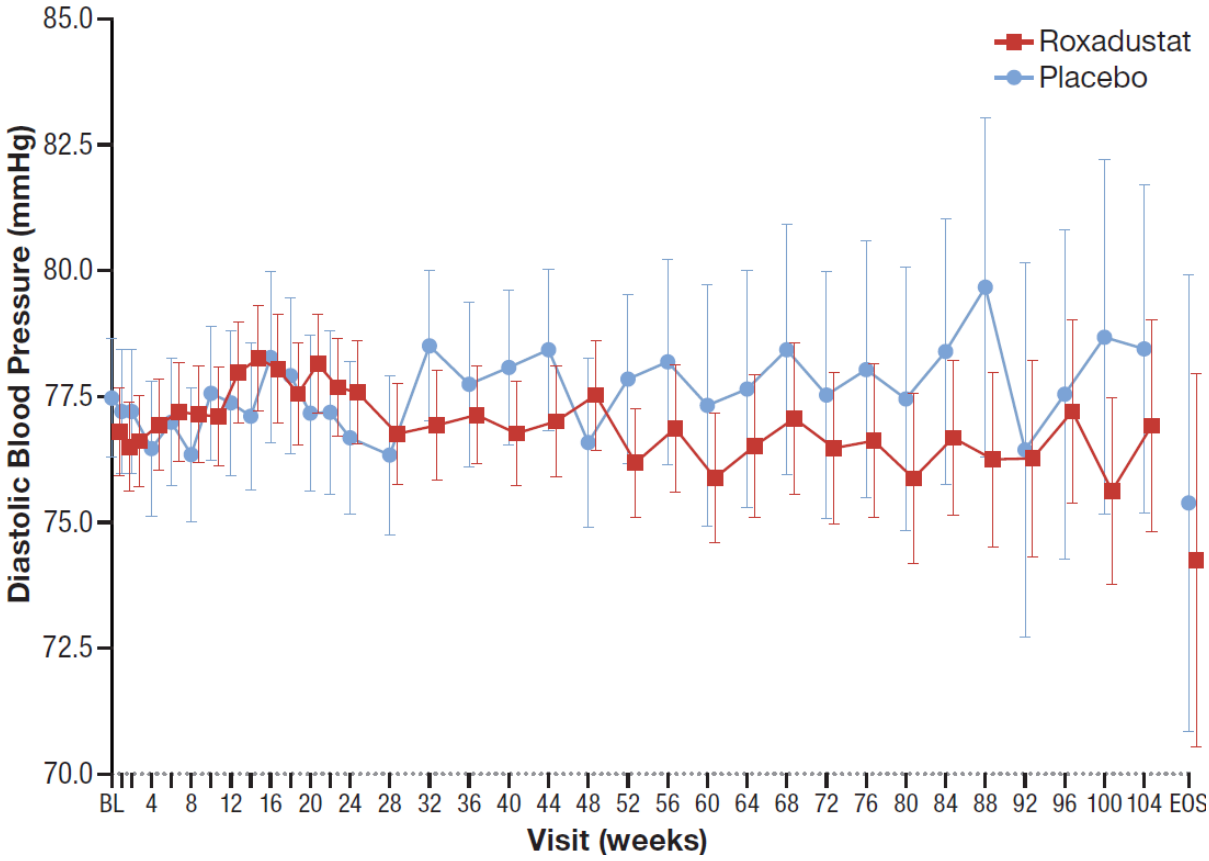
Abbreviation: CI, confidence interval; EOS, end of study.

Supplemental Figure 12. Mean (± 95% CI) Plot of Systolic Blood Pressure (mmHg), Safety Analysis Set



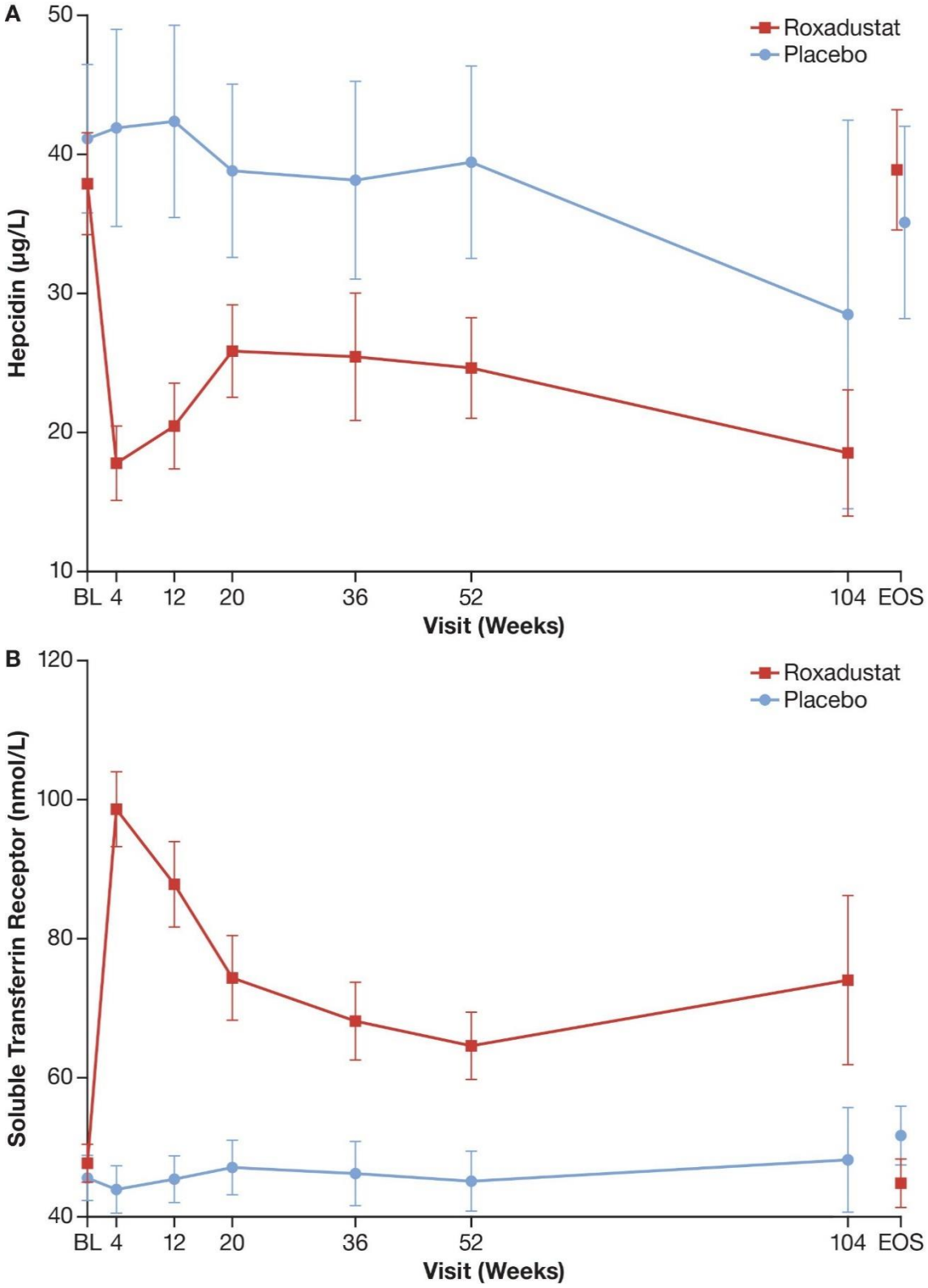
Abbreviation: CI, confidence interval; EOS, end of study.

Supplemental Figure 13. Mean (± 95% CI) Plot of Diastolic Blood Pressure (mmHg), Safety Analysis Set



Abbreviation: CI, confidence interval; EOS, end of study.

Supplemental Figure 14. Mean (± 95% CI) Plot of Hepcidin (A) and Soluble Transferrin Receptor (B) by Visit (Full Analysis Set)



Abbreviations: CI, confidence interval; EOS, end of study.

Supplemental Table 1. Fixed Sequence Testing Procedure for Key Secondary Endpoints (FAS Set)

Test Sequence	Variable	Analysis Method	Analysis Set	Test Type	Statistics (units)	Result 95% CI *P*-value	Null Hypothesis Status
Key secondary 1	Hb change from baseline to the average Hb (g/dL) in Weeks 28-36	MMRM	FAS	Superiority	Difference of LSM (g/dL)	1.599 (1.41, 1.78) *P*<0.001	Rejected
Key secondary 2	Change from baseline in LDL cholesterol to the average LDL cholesterol (mmol/L) in Weeks 12-28	MMRM	FAS	Superiority	Difference of LSM (mmol/L)	-0.701 (-0.83, -0.57) *P*<0.001	Rejected
Key secondary 3	Time to first use of rescue therapy during the efficacy-emergent period	Stratified Cox proportional hazards	FAS	Superiority	Hazard ratio	0.238 (0.17, 0.33) *P*<0.001	Rejected
Key secondary 4	Change from baseline in SF-36 VT subscore to the average SF-36 VT in Weeks 12-28	MMRM	FAS	Superiority	Difference of LSM (points)	1.127 (-0.19, 2.44) *P*=0.093	Not rejected
Key secondary 5	Change from baseline in SF-36 PF subscore to the average SF-36 PF in Weeks 12-28	MMRM	FAS	Superiority	Difference of LSM (points)	0.713 (-0.56, 1.98) *P*=0.270	Not rejected

All the analyses compare roxadustat vs placebo.
Abbreviations: CI, confidence interval; FAS, full analysis set; Hb, hemoglobin; LDL, low-density lipoprotein; LSM, least square means; MAP, mean arterial pressure; MMRM, mixed model repeated measures; SF-36 PF, Short Form 36 Physical Function Health questionnaire; SF-36 VT, Short Form 36 Vitality Health questionnaire.

Supplemental Table 2. Schedule of Assessments

Study Period:	**Screening**			**Treatment[a]**				**Follow-up**				**Poststudy Follow-up**
Visit/Week:	**Up to 6 Weeks** **S1**	**S2**	**S3**	**Day 1[b]**	**Weekly** (wks 1 to 2) ± 2 days	**Every 2 Weeks** (wks 4 to 24) ± 2 days	**Every 4 Weeks** (wks 28 to 100) ± 3 days	**EOT** (wk 104) ± 3 days	**EOT + 2 wks** ± 3 days	**EOS** (EOT **+ 4 wks**) ± 3 days	**Unscheduled Visits**	Every 6 months until projected wk 108
Written informed consent	X											
Randomization				X								
Eligibility criteria	X			X								
Demographics and medical history including tobacco use	X											
Weight	X			X		wks 12, 24	wks 36, 52, 76	X		X	O[c]	
Physical examination	X			X		wks 12[d] 24[d]	wks 36[d], 52[d], 76[d]	X		X[c]	O[c, d]	
Blood pressure[e], heart rate[e], respiratory rate[g]	X	X	X	X	X	X	X	X		X	O[c]	
CBC with WBC differential, red cell indices and platelet count	X			X	X	wks 4, 8, 12, 20	wk 28 and every following 8 wks	X		X	O[c]	
Reticulocyte count, hemoglobin content of reticulocytes (CHr)	X			X	X	wks 4, 6, 8, 12, 16, 20	wk 28 and every following 8 wks	X		X	O[c]	
Hemoglobin[h]		X	X			X	X		X		O[c]	
HemoCue® assessment[i]				X	X	X	X				O[c]	
Serum chemistry (incl LFT)	X			X		wks 4, 8, 12, 20	wk 28 and every following 8 wks	X	X	X	O[c]	
LFTs[j]					wk 2	wks 6, 16					O[c]	
Serum lipid panel (fasting whenever possible)	X			X		wks 4, 8, 12, 20	wks 28, 36, 44, 52, 68, 84	X		X	O[c]	
Serum iron, ferritin, TIBC, TSAT	X			X		wks 4, 8, 12, 20	wk 28 and every following 8 wks	X		X	O[c]	
HbA1c	X			X		wk 12	wks 28, 36, 44, 60, 84	X		X	O[c]	
Vitamin B_{12}, folate	X											
HIV immunoassay, HBsAg, anti-HCV antibody	X											
Serum pregnancy test[k]	X					wks 12, 24	wks 36, 48, 60, 72, 84, 96	X			O[c]	
eGFR (Cr Clear Modified Diet Abbreviated)[l]	X			X		wk 20	wks 36, 52, 68, 84	X		X	O[c]	
Special laboratory analytes (hepcidin, sTfR, hs-CRP)				X		wks 4, 12, 20	wks 36, 52	X		X		
Archival serum/plasma samples for biomarkers				X		wks 4, 12, 20	wks 52, 76	X		X		

Study Period:	**Screening**			**Treatment[a]**				**Follow-up**				**Poststudy Follow-up**
Visit/Week:	**Up to 6 Weeks** **S1**	**S2**	**S3**	**Day 1[b]**	**Weekly** (wks 1 to 2) ± 2 days	**Every 2 Weeks** (wks 4 to 24) ± 2 days	**Every 4 Weeks** (wks 28 to 100) ± 3 days	**EOT** (wk 104) ± 3 days	**EOT + 2 wks** ± 3 days	**EOS** (EOT **+ 4 wks**) ± 3 days	**Unscheduled Visits**	Every 6 months until projected wk 108
Blood sample for population pharmacokinetics					wks 2 to 8[m]							
Genotyping[n]					X							
Urinary testing[o]				X		wks 12, 24	wks 36, 52, 64, 76, 88	X			O[c]	
Quality of Life Questionnaires[p]				X		wks 8, 12	wks 28, 36, 52, 76	X			O[c]	
12-lead ECG	X			X		wks 12, 24	wks 36, 52, 76	X			O[c]	
Renal ultrasound[q]	X										O[c]	
Dose adjustment review[r]						X	X				O[c]	
Hospitalization recording[s]	X	X	X	X	X	X	X	X	X	X	X	X
AE recording	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medication recording	X	X	X	X	X	X	X	X	X	X	X	
Procedure and nondrug therapy recording	X	X	X	X	X	X	X	X	X	X	X	
Study drug dispensing[t]				X[u]	X	X	X				O[c]	
Vital status, SAEs, cardiovascular and thromboembolic AEs												X

Abbreviations: AE, adverse events; CBC, complete blood count; CHr, hemoglobin content of reticulocytes; Cr, creatinine; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; EOT, end of treatment; EOS, end of study; HbA1c, hemoglobin A1c glycated hemoglobin; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; hs-CRP, high-sensitivity C-reactive protein; LFT, liver function test; O, optional test/assessment (see below for footnotes); S1/S2/S3, screening visit 1, 2, and 3; SAE, serious adverse event; sTfR, soluble transferrin receptor; TIBC, total iron binding capacity; TSAT, transferrin saturation (also known as FeSAT, iron saturation); WBC, white blood cell; wk(s), week(s); X, mandatory test/assessment.

Table footnotes continued on next page

[a] In case of premature discontinuation or withdrawal during the treatment period, the patient was to complete the EOT visits (EOT visit and EOT + 2 weeks visit) and the EOS visit. Thereafter, this patient continued to be followed up every 6 months for vital status and SAEs, cardiovascular, and thromboembolic AEs until their projected date of completion (ie, projected Week 108 date) or, if earlier, until the last patient randomized reached EOS, or until consent was withdrawn.
[b] All study assessments were performed prior to first study drug administration.
[c] The study drug dosing was to be reviewed and, if needed, new or additional study drug was to be dispensed.
[d] Targeted physical examination only (eg, respiratory and cardiovascular).
[e] Blood pressure measured singly during the screening period, and in triplicate at all other visits. It was recommended during the treatment period that BP measurement should occur prior to study drug administration if study medication was taken on same day of visit, except for visits where patients were instructed to take study medication at home for pharmacokinetic sampling purpose. For patients requiring dialysis, BP was recorded prior to and after dialysis (hemodialysis [HD]/hemodiafiltration [HDF] patients only).
[f] Heart rate (HR) measured singly during the screening period, and in triplicate at all other visits. It was recommended during the treatment period that HR measurement should occur prior to study drug administration if study medication was taken on the same day of visit, except for visits where patients were instructed to take study medication at home for pharmacokinetic sampling purposes. For patients requiring dialysis, HR was recorded prior to and after dialysis (HD/HDF patients only).
[g] Respiratory rate measured singly during all visits. It was recommended during the treatment period that respiratory rate measurement should occur prior to study drug administration, except for visits where patients were instructed to take study medication at home for pharmacokinetic sampling purposes. For patients requiring dialysis, respiratory rate was recorded prior to dialysis (HD/HDF patients only).
[h] Hemoglobin (Hb) was collected at all the visits where CBC was not collected.
[i] If during an unscheduled visit Hb needed to be assessed, this was always done with the HemoCue AND central laboratory Hb assessment. Hb was assessed by HemoCue on the blood sample collected for central laboratory Hb assessment.
[j] Liver function tests were collected at visits where full serum chemistry was not collected.
[k] Collected from female patients of childbearing potential only.
[l] Calculated by the Central Laboratory.
[m] Sampling of roxadustat was done at six timepoints over 1-3 visits. At each pharmacokinetic visit, an additional sample was collected for albumin and alpha-acid glycoprotein determination.
[n] Optional assessment. A separate informed consent form was signed before a genotyping sample was collected. Sample collection could be done at any timepoint throughout the treatment period of the study
[o] Ideally, the sample was to be from the first morning void. Urinary testing included qualitative testing with dipstick testing (for protein, pH, glucose) and quantitative assessment of albumin and Cr for calculation of albumin/Cr ratio. At Day 1, Weeks 24, 52, and 76, and EOT, a urine sample was archived for potential future biomarker analysis.
[p] The Quality of Life (QoL) Questionnaires used were SF-36, FACT-An, EQ-5D-5L, PGIC, and WPAI:AnS. The PGIC questionnaire was not completed at Day 1. Questionnaires were to be completed by the patient, preferably prior to any study assessments. When patients needed dialysis therapy, QoL Questionnaires were completed on the day of first dialysis (preferably before the dialysis was started), 4 weeks later, and 12 weeks later.
[q] Renal ultrasound examination within 12 weeks of randomization. Not required if result of a previous renal ultrasound (or other imaging modality such as CT scan or magnetic resonance imaging) within 12 weeks prior to randomization is available and ruled out renal cell carcinoma. If other imaging modality, a conclusive report on the kidney, was to be available.
[r] Dose adjustment review from Week 4 onward, and every 4 weeks thereafter, until EOT (except in the event of Hb rate of rise >2 g/dL within 4 weeks, or Hb ≥13.0 g/dL). If next dose adjustment interval fell on a non-visit study week, the dose adjustment review was to be performed at the next scheduled visit.
[s] Telephone or in-person follow-up call with patient.
[t] For patients requiring dialysis, it was recommended for HD/HDF patients that study drug was administered any time after completion of dialysis (if dosing was scheduled on a dialysis day).
[u] Intake of initial study drug on day of randomization.

Supplemental Table 3. Additional Demographics and Baseline Characteristics (Safety Analysis Set)

Parameter	Category/Statistic	Roxadustat (n=391)	Placebo (n=203)	Total (N=594)
Country	Belarus	7 (1.8%)	5 (2.5%)	12 (2.0%)
	Belgium	5 (1.3%)	4 (2.0%)	9 (1.5%)
	Bulgaria	24 (6.1%)	11 (5.4%)	35 (5.9%)
	Colombia	1 (0.3%)	2 (1.0%)	3 (0.5%)
	Dominican Republic	8 (2.0%)	4 (2.0%)	12 (2.0%)
	Estonia	0	1 (0.5%)	1 (0.2%)
	Georgia (Republic)	10 (2.6%)	7 (3.4%)	17 (2.9%)
	Greece	4 (1.0%)	2 (1.0%)	6 (1.0%)
	Guatemala	21 (5.4%)	6 (3.0%)	27 (4.5%)
	Hungary	7 (1.8%)	5 (2.5%)	12 (2.0%)
	Italy	4 (1.0%)	2 (1.0%)	6 (1.0%)
	Panama	6 (1.5%)	6 (3.0%)	12 (2.0%)
	Peru	2 (0.5%)	1 (0.5%)	3 (0.5%)
	Poland	34 (8.7%)	14 (6.9%)	48 (8.1%)
	Romania	30 (7.7%)	16 (7.9%)	46 (7.7%)
	Russian Federation	64 (16.4%)	34 (16.7%)	98 (16.5%)
	Serbia	56 (14.3%)	29 (14.3%)	85 (14.3%)
	South Africa	12 (3.1%)	4 (2.0%)	16 (2.7%)
	Spain	11 (2.8%)	6 (3.0%)	17 (2.9%)
	Turkey	15 (3.8%)	4 (2.0%)	19 (3.2%)
	United Kingdom	8 (2.0%)	4 (2.0%)	12 (2.0%)
	Ukraine	62 (15.9%)	36 (17.7%)	98 (16.5%)
Previous medications (≥10% patients in any treatment group)	Iron	198 (50.6%)	105 (51.7%)	303 (51.0%)
	Furosemide	139 (35.5%)	84 (41.4%)	223 (37.5%)
	Amlodipine	123 (31.5%)	73 (36.0%)	196 (33.0%)
	Acetylsalicylic acid	112 (28.6%)	53 (26.1%)	165 (27.8%)
	Folic acid	108 (27.6%)	53 (26.1%)	161 (27.1%)
	Allopurinol	97 (24.8%)	48 (23.6%)	145 (24.4%)
	Bisoprolol	98 (25.1%)	47 (23.2%)	145 (24.4%)
	Atorvastatin	67 (17.1%)	35 (17.2%)	102 (17.2%)
	Erythropoietin human	45 (11.5%)	24 (11.8%)	69 (11.6%)
	Losartan	48 (12.3%)	18 (8.9%)	66 (11.1%)
	Calcium carbonate	44 (11.3%)	21 (10.3%)	65 (10.9%)
	Sodium bicarbonate	47 (12.0%)	17 (8.4%)	64 (10.8%)
	Moxonidine	36 (9.2%)	25 (12.3%)	61 (10.3%)
	Lercanidipine	42 (10.7%)	16 (7.9%)	58 (9.8%)
	Metoprolol	34 (8.7%)	22 (10.8%)	56 (9.4%)
	Pantoprazole	34 (8.7%)	22 (10.8%)	56 (9.4%)
	Insulin human	23 (5.9%)	21 (10.3%)	44 (7.4%)
Medication for anemia	ESA	45 (11.5%)	24 (11.8%)	69 (11.6%)
	IV iron	33 (8.4%)	19 (9.4%)	52 (8.8%)
	Oral iron	152 (38.9%)	79 (38.9%)	231 (38.9%)
	Vitamin B12	21 (5.4%)	13 (6.4%)	34 (5.7%)
	Folate	71 (18.2%)	29 (14.3%)	100 (16.8%)
	Blood transfusion	11 (2.8%)	9 (4.4%)	20 (3.4%)
	Androgen	0	0	0
	Other	19 (4.9%)	7 (3.4%)	26 (4.4%)
Type of ESA	Epoetin alfa	17 (4.3%)	9 (4.4%)	26 (4.4%)
	Epoetin beta	6 (1.5%)	5 (2.5%)	11 (1.9%)
	Methoxy polyethylene glycol-epoetin beta	5 (1.3%)	3 (1.5%)	8 (1.3%)
	Darbepoetin alfa	12 (3.1%)	8 (3.9%)	20 (3.4%)
	Biosimilar ESA	5 (1.3%)	0	5 (0.8%)
	Other ESA	2 (0.5%)	0	2 (0.3%)

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

Supplemental Table 4. Change from Baseline in LDL Cholesterol (mmol/L) Regardless of Fasting Status in Patients Using Statins (Full Analysis Set)

	Roxadustat (N=119)		**Placebo (N=61)**	
	n	Mean (SD)	n	Mean (SD)
BL	119	2.486 (1.138)	61	2.324 (0.926)
Change from BL to average in Weeks 12-28	107	-0.368 (0.847)	56	0.326 (0.798)
Change from BL to end of study	78	-0.026 (1.054)	44	0.153 (0.805)

Abbreviations: BL, baseline; LDL, low-density lipoprotein; SD, standard deviation

Supplemental Table 5. Time to First Use of Rescue Therapy During the Efficacy-Emergent Period (Full Analysis Set)

	Roxadustat (n=389)	**Placebo (n=203)**
Number of patients with rescue therapy, n (%)†	64 (16.5%)	93 (45.8%)
Red blood cells	31 (8.0%)	34 (16.7%)
Intravenous iron	21 (5.4%)	12 (5.9%)
ESA	12 (3.1%)	47 (23.2%)
Cumulative time at risk (years)	438.5	155.9
Incidence rate (per 100 patient-years at risk)	14.6	59.6
Hazard ratio‡	0.238	
95% CI	(0.17, 0.33)	
P-value	*P*<0.001	

The efficacy-emergent period is defined as the evaluation period from the analysis date of first dose intake up to 7 days after the analysis date of the last dose or the end of trial visit, whichever occurs first.

† For patients who have experienced more than one rescue therapy (ie, red blood cell, IV iron, and ESA), only their first event following study treatment is used.

‡ Hazard ratio is calculated using stratified Cox proportional hazards regression, stratifying on cardiovascular history and region and adjusting on Hb and eGFR at baseline as continuous covariates. Superiority is declared if the upper bound of the 95% CI is below 1.0.

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; IV, intravenous.

Supplemental Table 6. Change from Baseline in Cholesterol and Apolipoproteins (Full Analysis Set)

	Roxadustat (N=389)		Placebo (N=203)	
	n	Mean (SD)	n	Mean (SD)
Cholesterol (mmol/L)				
BL	389	4.989 (1.586)	203	4.856 (1.442)
Change from BL to Week 8	348	-1.066 (1.086)	191	0.048 (0.932)
Change from BL to Week 28	310	-0.816 (1.284)	149	0.201 (1.271)
Change from BL to Week 52	278	-0.815 (1.314)	120	0.104 (1.304)
Change from BL to Week 104	123	-0.944 (1.584)	32	0.218 (1.067)
LDL cholesterol (mmol/L)				
BL	389	2.985 (1.285)	203	2.883 (1.142)
Change from BL to Week 8	348	-0.743 (0.896)	190	0.048 (0.736)
Change from BL to Week 28	310	-0.584 (1.026)	149	0.203 (0.944)
Change from BL to Week 52	278	-0.629 (1.118)	120	0.059 (0.979)
Change from BL to Week 104	122	-0.709 (1.336)	32	0.126 (0.865)
LDL/HDL cholesterol ratio				
BL	389	2.824 (1.774)	203	2.770 (1.777)
Change from BL to Week 8	347	-0.374 (0.952)	190	0.068 (0.685)
Change from BL to Week 28	309	-0.313 (1.057)	149	0.156 (0.861)
Change from BL to Week 52	277	-0.429 (1.125)	120	0.019 (1.076)
Change from BL to Week 104	122	-0.414 (1.306)	32	0.105 (0.873)
Non-HDL cholesterol (mmol/L)				
BL	389	3.839 (1.565)	203	3.711 (1.415)
Change from BL to Week 8	347	-0.909 (1.064)	190	0.070 (0.864)
Change from BL to Week 28	309	-0.710 (1.227)	149	0.206 (1.227)
Change from BL to Week 52	277	-0.751 (1.276)	120	0.104 (1.299)
Change from BL to Week 104	123	-0.839 (1.554)	32	0.174 (1.014)
HDL cholesterol (mmol/L)				
BL	389	1.149 (0.347)	203	1.142 (0.332)
Change from BL to Week 8	348	-0.158 (0.225)	191	-0.013 (0.209)
Change from BL to Week 28	310	-0.109 (0.282)	149	0.001 (0.221)
Change from BL to Week 52	278	-0.064 (0.276)	120	0.008 (0.261)
Change from BL to Week 104	123	-0.104 (0.263)	32	0.043 (0.260)
Apolipoprotein A1 (mg/dL) †				
BL	188	1.355 (0.313)	105	1.335 (0.296)
Change from BL to Week 8	174	-0.148 (0.229)	102	0.008 (0.227)
Change from BL to Week 28	134	-0.104 (0.265)	67	0.006 (0.233)
Change from BL to Week 52	139	-0.090 (0.260)	71	-0.028 (0.248)
Change from BL to Week 104	12	-0.098 (0.227)	4	0.070 (0.136)
Apolipoprotein B (mgd/L) †				
BL	188	91.888 (31.995)	105	89.800 (31.979)
Change from BL to Week 8	174	-19.483 (21.009)	102	2.059 (20.297)
Change from BL to Week 28	133	-13.782 (28.634)	67	9.746 (26.864)
Change from BL to Week 52	139	-14.122 (27.503)	71	4.676 (31.440)
Change from BL to Week 104	12	-10.917 (22.885)	4	14.750 (20.271)
Apolipoprotein B/Apolipoprotein A1 ratio †				
BL	188	0.705 (0.265)	104	0.732 (0.416)
Change from BL to Week 8	172	-0.084 (0.202)	101	0.000 (0.184)
Change from BL to Week 28	133	-0.066 (0.222)	66	0.063 (0.205)
Change from BL to Week 52	137	-0.065 (0.207)	70	0.047 (0.266)
Change from BL to Week 104	12	-0.024 (0.126)	4	0.085 (0.132)
Triglycerides (mmol/L)				
BL	389	1.827 (1.142)	203	1.756 (1.136)
Change from BL to Week 8	348	-0.239 (0.829)	191	0.065 (0.929)
Change from BL to Week 28	310	-0.173 (1.000)	149	0.040 (1.035)
Change from BL to Week 52	278	-0.204 (0.933)	120	0.132 (1.162)
Change from BL to Week 104	123	-0.136 (1.096)	32	0.128 (0.948)

Baseline is defined as the value on Day 1. If this value was missing, the latest value prior to first study drug administration was used.

† Apolipoprotein values were not recorded for all patients.

Abbreviations: BL, baseline; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SD, standard deviation.

Supplemental Table 7. Common (≥1% Patients in Any Treatment Group) Serious Treatment-Emergent Adverse Event During the Safety Emergent Period (Safety Analysis Set)

MedDRA v20.0 System Organ Class Preferred Term	Roxadustat (N=391; PEY=496.9)		Placebo (N=203; PEY=210.0)	
	n (%)	#E (Event rate per 100 PEY)	n (%)	#E (Event rate per 100 PEY)
Overall	241 (61.6%)	515 (103.6)	115 (56.7%)	250 (119.0)
Renal and urinary disorders	**145 (37.1%)**	**157 (31.6)**	**70 (34.5%)**	**77 (36.7)**
End stage renal disease	135 (34.5%)	135 (27.2)	62 (30.5%)	63 (30.0)
Azotaemia	10 (2.6%)	11 (2.2)	8 (3.9%)	10 (4.8)
Acute kidney injury	1 (0.3%)	1 (0.2)	2 (1.0%)	3 (1.4)
Infections and infestations	**53 (13.6%)**	**82 (16.5)**	**25 (12.3%)**	**29 (13.8)**
Pneumonia	17 (4.3%)	21 (4.2)	12 (5.9%)	14 (6.7)
Sepsis	6 (1.5%)	6 (1.2)	0	0
Peritonitis	5 (1.3%)	6 (1.2)	1 (0.5%)	1 (0.5)
Pyelonephritis chronic	5 (1.3%)	5 (1.0)	2 (1.0%)	2 (1.0)
Device related infection	4 (1.0%)	5 (1.0)	0	0
Cardiac disorders	**33 (8.4%)**	**39 (7.8)**	**14 (6.9%)**	**25 (11.9)**
Myocardial infarction	8 (2.0%)	8 (1.6)	3 (1.5%)	3 (1.4)
Acute myocardial infarction	6 (1.5%)	6 (1.2)	2 (1.0%)	2 (1.0)
Atrial fibrillation	3 (0.8%)	3 (0.6)	3 (1.5%)	3 (1.4)
Cardiac failure chronic	3 (0.8%)	3 (0.6)	3 (1.5%)	4 (1.9)
Coronary artery disease	1 (0.3%)	1 (0.2)	2 (1.0%)	2 (1.0)
Injury, poisoning and procedural complications	**26 (6.6%)**	**33 (6.6)**	**5 (2.5%)**	**5 (2.4)**
Arteriovenous fistula thrombosis	14 (3.6%)	17 (3.4)	0	0
Hip fracture	4 (1.0%)	4 (0.8)	0	0
Investigations	**23 (5.9%)**	**26 (5.2)**	**11 (5.4%)**	**15 (7.1)**
Glomerular filtration rate decreased	21 (5.4%)	23 (4.6)	11 (5.4%)	15 (7.1)
Vascular disorders	**22 (5.6%)**	**24 (4.8)**	**8 (3.9%)**	**9 (4.3)**
Deep vein thrombosis	4 (1.0%)	4 (0.8)	0	0
Hypertension	4 (1.0%)	4 (0.8)	1 (0.5%)	2 (1.0)
Hypertensive crisis	4 (1.0%)	4 (0.8)	5 (2.5%)	5 (2.4)
Nervous system disorders	**21 (5.4%)**	**24 (4.8)**	**10 (4.9%)**	**10 (4.8)**
Cerebrovascular accident	5 (1.3%)	5 (1.0)	0	0
Ischaemic stroke	4 (1.0%)	4 (0.8)	1 (0.5%)	1 (0.5)
Diabetic neuropathy	0	0	2 (1.0%)	2 (1.0)
Respiratory, thoracic and mediastinal disorders	**21 (5.4%)**	**23 (4.6)**	**13 (6.4%)**	**18 (8.6)**
Pleural effusion	3 (0.8%)	4 (0.8)	3 (1.5%)	5 (2.4)
Pulmonary oedema	3 (0.8%)	3 (0.6)	2 (1.0%)	2 (1.0)
Hydrothorax	0	0	2 (1.0%)	3 (1.4)
Metabolism and nutrition disorders	**16 (4.1%)**	**20 (4.0)**	**7 (3.4%)**	**8 (3.8)**
Hyperkalaemia	4 (1.0%)	4 (0.8)	2 (1.0%)	2 (1.0)
Diabetic metabolic decompensation	1 (0.3%)	1 (0.2)	2 (1.0%)	2 (1.0)
General disorders and administration site conditions	**11 (2.8%)**	**11 (2.2)**	**13 (6.4%)**	**14 (6.7)**
Death	4 (1.0%)	4 (0.8)	3 (1.5%)	3 (1.4)
Asthenia	1 (0.3%)	1 (0.2)	2 (1.0%)	2 (1.0)
Multiple organ dysfunction syndrome	1 (0.3%)	1 (0.2)	2 (1.0%)	2 (1.0)
Catheter site haemorrhage	0	0	2 (1.0%)	2 (1.0)
Peripheral swelling	0	0	2 (1.0%)	2 (1.0)
Blood and lymphatic system disorders	**11 (2.8%)**	**13 (2.6)**	**11 (5.4%)**	**14 (6.7)**
Anaemia	8 (2.0%)	10 (2.0)	7 (3.4%)	9 (4.3)

#E: number of events; PEY: patient exposure years.
Event rate per 100 PEY is defined as (number of events)*100 divided by PEY during safety-emergent period.
Sorting order: incidence by System Organ Class (SOC), then incidence by Preferred Term (PT).
SOCs presented where they include a PT where threshold of ≥1% of patients is exceeded in any treatment group.

Reference

1. Cella, D., *The Functional Assessment of Cancer Therapy-Anemia (FACT-An) Scale: a new tool for the assessment of outcomes in cancer anemia and fatigue.* Semin Hematol, 1997. **34**(3 Suppl 2): p. 13-9.