Pooled Analysis of Roxadustat for Anemia in Patients with Kidney Failure Incident to Dialysis

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Supplementary Material

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SUPPLEMENTARY METHODS

Study Drug Dosing
Study 063 recruited only ID-DD CKD patients that were ESA-naïve at the time of randomization, with the exception of ID-DD CKD patients recruited in the US after protocol amendment 2; these US patients were allowed to receive ESA maximum up to 3 weeks in the 12 weeks prior to screening. However, no ESA was allowed during screening. The starting dose was 70 mg for patients weighing ≤70 kg and 100 mg for patients weighing >70–160 kg, thrice weekly (TIW). Dose adjustments occurred in a Correction Phase (with the goal of attaining targeted hemoglobin range of 10–12 g/dl) and a Maintenance Phase (with the goal of maintaining the hemoglobin in the target range). The maximum roxadustat dose was 3.0 mg/kg per dose or 400 mg per administration (whichever was lower). Epoetin alfa was dosed according to the country-specific product labeling and doses were adjusted to maintain hemoglobin level at 10.0–11.0 g/dl (US) or 10.0–12.0 g/dl (ex-US).

For patients taking an ESA at study entry—which included all Study 064 patients and most Study 002 participants—a simplified conversion chart based on average weekly ESA dosing totals was used to determine roxadustat starting doses. If the mean qualifying screening hemoglobin value at randomization was <10 g/dl, the starting roxadustat dose was increased by 1 dose step. Patients in Study 002 not taking an ESA at study entry initiated roxadustat using a tiered, weight-based dosing scheme.

During the Treatment Period of Study 064 and 002, roxadustat dose adjustments were made according to the dose adjustment algorithm to maintain a hemoglobin level of approximately 11 g/dl. Roxadustat dose adjustments were permitted from Week 4 onwards, and every 4 weeks thereafter; however, a dose adjustment was allowed between two prespecified windows if no dose adjustment was made in the prior four weeks and hemoglobin was <9.0 g/dl. Patients were to take doses TIW for the entire duration of the Treatment Period. If a patient required <20 mg TIW to maintain a hemoglobin level of approximately 11 g/dl, the dosing frequency was reduced in a stepwise fashion. If a hemoglobin rise of >2 g/dl occurred within 4 weeks, the dose was reduced by 1 dose step. If the hemoglobin level was ≥13 g/dl at any time, the dose was placed on hold until hemoglobin decreased to <12.0 g/dl. The maximum roxadustat dose was 3.0 mg/kg per dose or 400 mg per administration (whichever was lower).

In Study 064, patients in to the epoetin alfa arm taking non-epoetin alfa treatments were switched to epoetin alfa treatment on Day 1. All subjects on HD received IV epoetin alfa TIW starting from Day 1, irrespective of their baseline route of administration or frequency of ESA use. The initial epoetin alfa dose was determined using a conversion table based on previous mean ESA dose. Subsequent epoetin alfa dosing and dose adjustments during the study, if indicated, were based on the country-specific Package Insert or Summary of Product Characteristics (SmPC).

In Study 002, for patients taking an ESA at study entry, the initial epoetin alfa dose was the actual dose administered at the first screening visit. Patients treated with darbepoetin alfa or methoxy polyethylene glycol epoetin beta prior to study entry initially received epoetin alfa at doses based on a conversion factor. For patients not taking an ESA, the initial dose of epoetin alfa was 50 IU/kg TIW. Epoetin alfa was dosed TIW, except for patients treated with epoetin alfa in a less frequent regimen prior to study entry. Dose adjustments occurred every 4 weeks or more and were consistent with local approved prescribing information or SmPC.
**IV Iron Supplementation**

- **Study 063**: in patients receiving roxadustat, the Investigator was allowed to initiate the use of an approved IV iron supplement if: the patient’s hemoglobin value had not sufficiently responded to ≥2 dose increases of roxadustat and ferritin <100 ng/ml or TSAT <20%.

- **Study 064**: IV iron supplementation was permitted if, in the opinion of the investigator, the patient had not adequately responded to oral iron, was not able to tolerate oral iron, and was considered iron deficient. IV iron was administered per local standard of care as deemed necessary by the investigator (Protocol Amendment 2).

- **Study 002**: in patients receiving roxadustat, the Investigator was allowed to initiate the use of an approved IV iron supplement if: the patient’s hemoglobin value had not sufficiently responded to ≥2 dose increases of roxadustat and ferritin <100 ng/ml or TSAT <20%.

**CV Safety Endpoint Definitions**

- **MACE**: a composite endpoint of myocardial infarction (MI), stroke, and all-cause mortality (ACM)
- **MACE+**: a composite endpoint of MI, stroke, ACM, hospitalization for unstable angina, and hospitalization for congestive heart failure (CHF)
- **MACE CV mortality**: death due to a CV cause, MI, or stroke
- **MACE+ CV mortality**: death due to a CV cause, MI, stroke, hospitalization for unstable angina, or hospitalization for CHF

The individual components of MACE and MACE+ are defined in the 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials.

For a specific type of mortality (such as CV death), patient follow-up time was from the first dose of study drug to the date of death due to the cause of interest or censored on the date of death due to other causes or the last date when the patient was known alive as defined above.

**Adjudication Process**

Owing to the importance of the determination of CV events for primary safety analyses, the Sponsor ensured that reported CV 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 (PSS) 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.

The purpose of this systematic, central, blinded adjudication process was to provide, to the greatest degree feasible, data for an accurate, consistent, and unbiased view of the CV safety profile of roxadustat vs. epoetin alfa in the pooled ID-DD patient population (Studies 063, 064, and 002). Events that occurred were adjudicated to determine whether each met a common
definition of MI, stroke, hospitalized unstable angina, hospitalized CHF, hypertensive emergency, deep venous thrombosis/pulmonary embolism, or vascular access thrombosis. The date and cause of deaths also were adjudicated. Events were selected based on pre-specified standard Medical Dictionary for Regulatory Activities (MedDRA) queries, specific for each type of event run against the Global Safety Database.

A summary of the process flow is as follows:

- Once a potential CV event was identified and reported by Global Safety Database, the necessary source documents were collected and submitted to the IERC Coordination Center (ICC) to start the adjudication process. If the ICC determined that the source documents were incomplete, the PSS was notified to initiate the process of collecting source documentation from the site in support of the event. After medical review, query resolution, anonymization, and blinding (to obscure key identifying information including patient identifiers and treatment assignment, blood transfusion, and hemoglobin, hematocrit, and RBC levels) were completed at the ICC, the redacted potential event package was released to the IERC for adjudication.

- Each potential event package was reviewed and adjudicated by two IERC members in an expedient manner in accordance with the charter. If there were concordant adjudications, the adjudication of the event was complete. If there was a minor adjudication discordance, the two members met to discuss and reach a consensus; if there was a major discordance, the IERC chairperson assisted the team to arrive at a final adjudication.

- CV events that included MACE and MACE+ are clearly defined and clarified in substantial detail in the IERC charter. One IERC chairperson oversees the CV, neurology, and nephrology sub-committees of physician IERC members who receive training to evaluate each potential event package independently using the supplied definitions.

Statistical Analyses

Efficacy Endpoints

The key US efficacy endpoint analysis was conducted on the ITT population (all randomized patients); secondary endpoint analyses were performed on the full analysis set (FAS; all randomized patients who received ≥1 dose of study drug and had ≥1 post-dose hemoglobin assessment). For a key EU efficacy endpoints, analyses were conducted on the FAS; analyses for non-inferiority were conducted on the per-protocol set (PPS; all FAS patients who received ≥8 weeks of treatment, had ≥1 valid post-dose hemoglobin assessment, and were without major protocol violations).

For the efficacy analysis, a multiple imputation analysis of covariance (ANCOVA) model was used, including terms for treatment group, baseline hemoglobin, and stratification factors (except screening hemoglobin ≤8.0 vs. >8.0 g/dl). At least 600 patients provided ≥99% power to show statistical non-inferiority of roxadustat vs. epoetin alfa for the US efficacy endpoint, assuming the following: a treatment group difference (roxadustat – epoetin alfa) of −0.30 g/dl, a non-inferiority margin for this difference of −0.75 g/dl, and a standard deviation of 1.25 g/dl. For the EU efficacy endpoint, the study provided ≥99% power to demonstrate statistical non-inferiority of roxadustat vs. epoetin alfa, assuming an 80% response rate for both treatment groups and a non-inferiority margin of −15% for the between-group difference (roxadustat – epoetin alfa).
A pattern-mixture model using a last mean carried forward multiple imputation method\textsuperscript{24} was used to explore the robustness of the ANCOVA results for the efficacy variables. Using this method, missing data after ending week were imputed based on the last non-missing mean from its own treatment group. The imputation process was repeated 200 times to generate 200 imputed data sets for the sensitivity analysis of key US and EU endpoints.

**CV Safety**

The primary statistical measure to determine non-inferiority of CV safety of roxadustat vs. epoetin alfa was the upper limit of the 95% CI of the pooled hazard ratio (HR) in the time-to-event analysis.

The pooled population HR was estimated using the meta-analysis method to combine the HRs from the individual studies. The algorithm for the meta-analysis method was:

Define

\[ LHR_i = \log(HR_i), \text{ the logarithm of hazard ratio comparing roxadustat with the comparator of } a; \]

\[ LVR_i = \text{ the variance of } LHR_i; \]

\[ W_i = 1/LVR_i. \]

The pooled log-hazard ratio, \( LHR_{\text{pool}} \), is calculated as

\[ LHR_{\text{pool}} = \sum_{i=1}^{k} W_i \times LHR_i / \sum_{i=1}^{k} W_i \]

The variance of \( LHR_{\text{pool}} \), \( V = 1/\sum_{i=1}^{k} W_i \).

Where \( k \) is the number of studies included in the pool.

The primary evaluation for this pooled analysis will be based upon a two-sided 95% CI, using the normal approximation of the log of the pooled hazard ratio, which is calculated as below:

The 2-sided 95% CI for the pooled hazard ratio then is calculated as:

\[ \exp [LHR_{\text{pool}} \pm Z_{\alpha/2} \times \sqrt{V}] . \]

Where \( \alpha = 0.05 \) and \( Z_{\alpha/2} = 1.96 \), the \( 1-\alpha/2 \) percentile of a standard normal distribution. p-value is computed as \( 2 \times [1 - \text{probnorm}(LHR_{\text{pool}}/\sqrt{V})] \).

For each of the DD studies (002, 063, 064), logarithm of the hazard ratio (LHR\(_i\)) and its variance were estimated using Cox regression modeling treatment effect, stratified by history of cardiovascular, cerebrovascular or thromboembolic diseases (Yes vs. No), geographic region (Europe vs. others), incident vs. stable dialysis, sex, BMI (<30 vs. \( \geq 30 \) kg/m\(^2\)), and race (black vs. other).

As an alternative to the meta-analysis method, an overall pooled model adding study identification as a model stratification factor also was evaluated. The primary evaluation window for the ID-DD populations was OT+7.
The individual components of MACE and MACE+ were analyzed using the primary analysis method per above. The number of events in some strata were small, and the Cox regression model was not stable. In these cases, descriptive statistics were used.

Subgroup Analyses
Time to MACE was analyzed using the primary method for the following subgroups:

1. Age group (<65 vs. ≥65 years)
2. Age group (<75 vs. ≥75 years)
3. Gender
4. Race (Asian, Black, White, Other)
5. Region (US vs. ex-US)
6. Region (Europe vs. ex-Europe)
7. Baseline BMI (<30 vs. ≥30 kg/m²)
8. Diabetes mellitus
9. History of cardiovascular, cerebrovascular, and thromboembolic diseases
10. History of coronary artery diseases
11. History of congestive heart failure
12. Baseline hs-CRP Level (≤ULN, >ULN)
13. Baseline hemoglobin level (<8 vs. ≥8 g/dl [ESA untreated] or <10 vs. ≥10 g/dl [ESA treated])
### Table S1. Summary of phase 3 clinical trials in patients with dialysis-dependent chronic kidney disease

| Study number          | Study 063 (FGCL-4592-063) | Study 064 (FGCL-4592-064) | Study 002 (D5740C00002) |
|-----------------------|---------------------------|---------------------------|--------------------------|
| **Study name**        | HIMALAYAS                 | SIERRAS                   | ROCKIES                  |
| **NCT number**        | NCT02052310               | NCT02273726               | NCT02174731              |
| **Sponsor**           | FibroGen                  | FibroGen                  | Astra Zeneca             |
| **Start date**        | February 11, 2014         | January 15, 2015          | July 1, 2014             |
| **Completion date**   | September 21, 2018        | September 19, 2018        | September 26, 2018       |
| **Design**            | Phase 3                   | Phase 3                   | Phase 3                  |
|                       | Multicenter (N=113, international) | Multicenter (N=76, US, Puerto Rico) | Multicenter (N=197, international) |
|                       | Randomized (1:1)          | Randomized (1:1)          | Randomized (1:1)         |
|                       | Open label                | Open label                | Open label               |
|                       | Active controlled         | Active controlled         | Active controlled        |
| **Patients**          | N=1043 (randomized)       | N=741 (randomized)        | N=2133                   |
| **Inclusion criteria**| Aged ≥18 y; weighing ≤160 kg | Aged ≥18 y; weighing 45-160 kg | Aged ≥18 y; weighing 45-160 kg |
|                       | On dialysis for KF 2 wk and ≤4 mo prior to randomization | On dialysis for KF ≥3 mo before/during screening | On dialysis for KF 30 d before Visit 1, (SDD) or On dialysis for KF ≥3 mo before/during screening and on stable ESA (≤30% Δ) during 4 wk before randomization |
|                       | Mean of 2 most recent Hb values ≤10.0 g/dl; high-low difference ≤1.3 g/dl (≥2 d apart) | Mean of 3 most recent Hb values ≥9.0 and ≤12.0 g/dl; high-low difference ≤1.3 g/dl (≥2 d apart) | Mean Hb <12.0 g/dl on 2 most recent visits (≥7 d apart) if on ESA at enrollment or Mean Hb <10.0 g/dl on 2 most recent visits (≥7 d apart) if not ESA-treated at enrollment |
|                       | Ferritin ≥100 ng/ml       | Ferritin ≥100 ng/ml       | Ferritin ≥100 ng/ml      |
|                       | TSAT ≥20%                 | TSAT ≥20%                 | TSAT ≥20%                |
|                       | Serum folate ≥LLN         | Serum folate ≥LLN         | Serum folate ≥LLN        |
|                       | Serum vitamin B12 ≥LLN    | Serum vitamin B12 ≥LLN    | Serum vitamin B12 ≥LLN   |
|                       | ALT/AST ≤3 × ULN and total bilirubin ≤1.5 × ULN | ALT/AST ≤3 × ULN and total bilirubin ≤1.5 × ULN | ALT/AST ≤3 × ULN and total bilirubin ≤1.5 × ULN |
|                       | No RBCT 4 wk before randomization | No RBCT ≤4 wk (Protocol Amendment 2) | No RBCT ≤4 wk (Protocol Amendment 2) |

**Intervention(s):**
- Roxadustat or epoetin alfa: TIW

**ID-DD subgroup:**
- On dialysis for KF 2 wk and ≤4 mo prior to randomization
- On ESA for ≥4 wk before screening
- Mean of 2 most recent Hb values ≥8.5 and ≤12.0 g/dl; high-low difference ≤1.3 (≥2 d apart)
Table S1. Summary of phase 3 clinical trials in patients with dialysis-dependent chronic kidney disease

| Study number: | Study 063 (FGCL-4592-063) | Study 064 (FGCL-4592-064) | Study 002 (D5740C00002) |
|---------------|-----------------------------|-----------------------------|-------------------------|
| **Mean (SD) drug exposure:** | **HIMALAYAS** | **SIERRAS** | **ROCKIES** |
| Roxadustat: 89.0 (±59.1) wk | Roxadustat: 88.1 (±59.7) wk | Roxadustat: 20.6 (±13.4) mo |
| Epoetin alfa: 96.0 (±61.9) wk | Epoetin alfa: 107.1 (±57.4) wk | Epoetin alfa: 23.2 (±12.7) mo |
| Mean Hb CFB averaged over W28-52 regardless of rescue therapy | Mean Hb CFB averaged over W28-52 regardless of rescue therapy | Mean Hb CFB averaged over W28-36 w/o rescue therapy|
| Mean Hb CFB averaged over W28-52 regardless of rescue therapy | Mean Hb CFB averaged over W28-36 w/o rescue therapy within 6 wk before and during this period | Mean Hb CFB averaged over W28-36 w/o rescue therapy within 6 wk before and during this period |
| **Primary US efficacy endpoint:** | **Primary EU efficacy endpoint:** | **Primary EU efficacy endpoint:** |
| Patients (%) w/Hb response (Hb ≥11.0 g/dl and Hb ↑ from BL ≥1.0 g/dl in those w/BL Hb >8.0 g/dl, or Hb ↑ ≥2.0 g/dl in those w/BL Hb ≤8.0 g/dl) at 2 consecutive visits ≥5 days apart during first 24 wk w/o rescue therapy within 6 wk of Hb response | Patients (%) w/Hb response (Hb ≥11.0 g/dl and Hb ↑ from BL ≥1.0 g/dl in those w/BL Hb >8.0 g/dl, or Hb ↑ ≥2.0 g/dl in those w/BL Hb ≤8.0 g/dl) at 2 consecutive visits ≥5 days apart during first 24 wk w/o rescue therapy within 6 wk of Hb response | Patients (%) w/Hb response (Hb ≥11.0 g/dl and Hb ↑ from BL ≥1.0 g/dl in those w/BL Hb >8.0 g/dl, or Hb ↑ ≥2.0 g/dl in those w/BL Hb ≤8.0 g/dl) at 2 consecutive visits ≥5 days apart during first 24 wk w/o rescue therapy within 6 wk of Hb response |
| **Safety assessments:** | **Safety assessments:** | **Safety assessments:** |
| TEAEs, TESAEs (nature, frequency, severity) | TEAEs, TESAEs (nature, frequency, severity) | TEAEs, TESAEs (nature, frequency, severity) |
| Vital signs, ECGs, and clinical laboratory | Vital signs, ECGs, and clinical laboratory | Vital signs, ECGs, and clinical laboratory |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BL, baseline; CFB, change from baseline; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; KF, kidney failure; LLN, lower limit of normal; RBCT, red blood cell transfusion; SDD, stable dialysis dependent; TEAE, treatment-emergent adverse events; TESAE, treatment-emergent serious adverse events; TIW, thrice weekly; TSAT, transferrin saturation; ULN, upper limit of normal; US, United States; W, week.

*Date first patient enrolled.
†Date the last patient completed the study.
‡In study 002, 27 patients were excluded from statistical analysis due to major Good Clinical Practice violations or technical issues.
Table S2. Patient numbers and exposure by study and overall

|                | Study 063 | Study 064 | Study 002 | Pooled Studies |
|----------------|-----------|-----------|-----------|----------------|
|                | Roxadustat| Epoetin alfa | Roxadustat| Epoetin alfa | Roxadustat| Epoetin alfa | Roxadustat| Epoetin alfa |
| Patients, n    | 522       | 517       | 36        | 35            | 202       | 214         | 760        | 770           |
| Patient exposure years* | 890.7     | 951.6     | 23.1      | 21.7          | 184.4     | 216.2       | 1098.2     | 1189.5        |
| Patient follow-up years† | 1025.2     | 1075.7     | 26.5      | 24.5          | 223.2     | 251.9       | 1274.9     | 1352.1        |

*Patient exposure years for each patient: (last dose date – first dose date + 1)/365.25.
†Patient follow-up years for each patient: (date of last known vital status – first dose date + 1)/365.25.
SUPPLEMENTARY FIGURES

Figure S1. Subgroup analysis for the key US efficacy endpoint (ITT)

| Category                  | LSM Difference (95% CI) |
|---------------------------|-------------------------|
| Overall                   | 0.22 (0.05, 0.40)       |
| **Sex**                   |                         |
| Male                      | 0.25 (0.04, 0.46)       |
| Female                    | 0.16 (−0.14, 0.47)      |
| **Age Group**             |                         |
| 18-64 years               | 0.21 (−0.01, 0.43)      |
| 65-74 years               | 0.42 (0.03, 0.82)       |
| ≥75 years                 | 0.05 (−0.40, 0.50)      |
| **Region**                |                         |
| US                        | 0.23 (0.01, 0.45)       |
| Europe                    | 0.16 (−0.02, 0.34)      |
| Other                     | 0.14 (−0.05, 0.34)      |
| **Iron status**           |                         |
| Replete                   | 0.24 (0.06, 0.43)       |
| Deficient                 | 0.12 (−0.39, 0.63)      |
| **Diabetes**              |                         |
| Yes                       | 0.26 (0.03, 0.48)       |
| No                        | 0.19 (−0.10, 0.48)      |
| **CRP**                   |                         |
| ≤ULN                      | 0.21 (−0.00, 0.43)      |
| >ULN                      | 0.32 (0.02, 0.62)       |
| **Hemoglobin**            |                         |
| <8 g/dL                   | 0.41 (0.08, 0.74)       |
| ≥8 g/dL                   | 0.20 (0.02, 0.37)       |
| **Body weight**           |                         |
| <70 kg                    | 0.18 (−0.11, 0.47)      |
| 70 to <100 kg             | 0.27 (−0.00, 0.54)      |
| ≥100 kg                   | 0.35 (−0.16, 0.85)      |

ANOVA, analysis of covariance; CI, confidence interval; CRP, C-reactive protein; Hb, hemoglobin; ITT, intent to treat; LSM, least-squares mean; ULN, upper limit of normal; US, United States.

Treatment comparison was made using the multiple imputation strategy by combining the results of ANCOVA model with baseline Hb as covariates, and study, treatment, study-by-treatment interaction, history of cardiovascular, cerebrovascular, and/or thromboembolic diseases (Yes vs. No) as fixed effects.
Figure S2. Subgroup analysis of MACE (OT+7*)

| Age Group | HR (95% CI)      |
|-----------|------------------|
| <65 years | 0.64 (0.42, 0.98) |
| ≥65 years | 0.81 (0.48, 1.37) |

| Gender | HR (95% CI)      |
|--------|------------------|
| Female | 0.95 (0.56, 1.62) |
| Male   | 0.61 (0.41, 0.90) |

| Race    | HR (95% CI)      |
|---------|------------------|
| Asian   | 0.63 (0.26, 1.56) |
| White   | 0.96 (0.66, 1.41) |

| Region  | HR (95% CI)      |
|---------|------------------|
| US      | 0.38 (0.20, 0.73) |
| Ex-US   | 0.86 (0.59, 1.24) |

| Region  | HR (95% CI)      |
|---------|------------------|
| Europe  | 1.20 (0.77, 1.87) |
| Ex-Europe | 0.39 (0.25, 0.63) |

| Baseline BMI | HR (95% CI)      |
|--------------|------------------|
| <30 or missing | 0.76 (0.53, 1.09) |
| ≥30          | 0.54 (0.26, 1.11) |

| Diabetes | HR (95% CI)      |
|----------|------------------|
| Yes      | 0.64 (0.42, 0.98) |
| No       | 0.71 (0.43, 1.19) |

| CV History† | HR (95% CI)      |
|-------------|------------------|
| Yes         | 0.81 (0.53, 1.22) |
| No          | 0.58 (0.35, 0.96) |

| CAD History | HR (95% CI)      |
|-------------|------------------|
| Yes         | 0.92 (0.54, 1.57) |
| No          | 0.66 (0.44, 0.99) |

| CHF History | HR (95% CI)      |
|-------------|------------------|
| Yes         | 0.89 (0.53, 1.51) |
| No          | 0.56 (0.37, 0.86) |

| Hs-CRP level | HR (95% CI)      |
|--------------|------------------|
| ≤ULN         | 0.71 (0.44, 1.16) |
| >ULN         | 0.86 (0.53, 1.38) |

| Baseline hemoglobin, g/dl | HR (95% CI)      |
|---------------------------|------------------|
| <10.0 (ESA treated) or <8.0 (ESA untreated) | 0.75 (0.47, 1.21) |
| ≥10.0 (ESA treated) or ≥8.0 (ESA untreated) | 0.74 (0.47, 1.16) |

BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; ULN, upper limit of normal; US, United States.

*OT+7: on treatment plus 7 days after the last dose of study drug.
†CV history includes cardiovascular, cerebrovascular, and thromboembolic disease.