

<b>Name of Sponsor/Company:</b> Astellas Pharma Europe B.V.		
<b>Name of Finished Product:</b> To be determined		
<b>Name of Active Ingredient:</b> Roxadustat		

## SYNOPSIS

**Title of Study:** A Phase 3, Randomized, Open-Label, Active-Controlled Study to Evaluate the Efficacy and Safety of Roxadustat in the Maintenance Treatment of Anemia in End Stage Renal Disease Patients on Stable Dialysis

**Investigators/Coordinating Investigator:** [REDACTED]

**Study Center(s):** 150 contracted sites in 17 countries: Belgium, Bulgaria, Croatia, Czech Republic, France, Georgia, Germany, Hungary, Italy, Poland, Portugal, Romania, Russian Federation, Serbia, Slovakia, Spain, and United Kingdom

**Publication Based on the Study:** Not applicable.

**Study Period:** Nov 2014 to Jul 2018

**Study Initiation Date (Date of First Enrollment):** 21 Nov 2014

**Study Completion Date (Date of Last Evaluation):** 06 Jul 2018

**Phase of Development:** 3

### Objectives:

#### *Primary Objective*

The primary objective of this study was to evaluate the efficacy of roxadustat compared to epoetin alfa and darbepoetin alfa in the maintenance treatment of anemia in end stage renal dialysis (ESRD) patients on stable dialysis.

#### *Secondary Objectives*

The secondary objectives in this study were to:

- Evaluate the safety of roxadustat compared to epoetin alfa and darbepoetin alfa in the maintenance treatment of anemia in ESRD patients on stable dialysis
- Evaluate the effects on health-related quality of life (HRQoL) of roxadustat compared to epoetin alfa and darbepoetin alfa in the maintenance treatment of anemia in ESRD patients on stable dialysis.

## Methodology:

This was a phase 3, multi-center, randomized, open-label, active-controlled study to assess the efficacy and safety of roxadustat treatment in adult patients with ESRD who were on stable hemodialysis (HD) or peritoneal dialysis (PD) and on stable treatment with epoetin (i.e., epoetin alfa, beta, theta, zeta, delta or omega) or darbepoetin alfa for anemia. The study consisted of 3 study periods: screening period (up to 42 days), treatment period (minimum of 52 weeks, maximum of 104 weeks) and a post-treatment follow-up period (4 weeks).

Eligible patients were randomized to 1 of 2 treatment groups. Treatment was given in an open-label manner.

- Treatment group 1: patients were switched from epoetin or darbepoetin alfa treatment to roxadustat treatment.
- Treatment group 2: patients continued erythropoiesis-stimulating agent (ESA) treatment, i.e., epoetin alfa if pretreated with any epoetin (i.e., epoetin alfa, beta, theta, zeta, delta or omega) or darbepoetin alfa if pretreated with darbepoetin alfa, at approximately the same average weekly dose that the patient was on prior to randomization. It was not allowed to switch from epoetin alfa to darbepoetin alfa or vice versa, during the treatment period.

Following the Screening Period, eligible patients who were randomized entered the Treatment Period (day 1).

Randomization and administration of the first dose of study treatment (roxadustat or ESA) was on day 1, which was to correspond to a day when the patients' next dose of epoetin or darbepoetin alfa would have been administered. The first dose of study treatment was taken after all study assessments had been completed; in HD patients only, study assessments were performed prior to or at initiation of dialysis (except for postdialysis weight and postdialysis vital signs).

For patients randomized to receive roxadustat, the initial roxadustat dose was based on the conversion table shown in Table 1 and was determined by the patient's average weekly dose of epoetin or darbepoetin alfa within 4 weeks prior to randomization.

**Table 1 Initial Dose of Roxadustat**

<b>Epoetin†</b> (IU/week)	<b>Darbepoetin Alfa†</b> (µg/week)	<b>Roxadustat</b> (mg/dose) TIW
< 8000	< 40	100
8000 to 16000	40 to 80	150‡
> 16000	> 80	200§

TIW: three times weekly.

† Average prescribed weekly dose in the last 4 weeks prior to randomization.

‡ If the initial dose of 150 mg exceeded the maximum dose of 3.0 mg/kg, then 100 mg was to be used as the starting dose.

§ If the initial dose of 200 mg exceeded the maximum dose of 3.0 mg/kg, then 150 mg was to be used as the starting dose.

Dose adjustments were permitted at 4-weekly intervals from week 4 onwards and were aimed at keeping patients' Hb levels between 10.0 to 12.0 g/dL and were based upon current hemoglobin (Hb) levels and change in Hb over the preceding 4 weeks. Deviation from the 4-week period was allowed anytime during the study in case of Hb rate of rise > 2 g/dL within 4 weeks or Hb  $\geq$  13.0 g/dL).

This study is part of a global phase 3 clinical development program and was adapted to support development in all regions worldwide. Following ongoing between development partners and regulatory agencies, the FDA and amendments to protocols in other ongoing studies in this program, the maximum dose of roxadustat was reduced from 3.5 mg/kg to 3.0 mg/kg in substantial amendment 1 (protocol v2.0) to align with the overall development program.

Patients that entered the study under protocol version 1.0, at the next scheduled visit, received a dose adjustment as needed according to the conversion table [Table 2].

**Table 2 Dose Adjustment for Roxadustat-treated Patients Moving from Protocol v1.0 to Protocol v2.0**

<b>Current TIW dose (mg)</b>	120	350
<b>If no dose titration needed</b>	100	300
<b>If up titration needed†</b>	150	400
<b>If down titration needed†</b>	100	300

TIW: three times weekly.

† Up or down titrations were only applicable when the criteria for dose adjustment have been met.

For patients randomized to receive ESA, the initial dose and frequency of administration were at the investigator's discretion provided that the average weekly dose remained approximately the same as prior to randomization.

### **Number of Patients (Planned, Enrolled and Analyzed):**

#### *Planned*

Approximately 750 patients were planned to be randomized to receive roxadustat or ESA in an open-label fashion in a 1:1 ratio.

#### *Enrolled and Analyzed*

A total of 1081 patients provided informed consent and were screened, of these patients, 838 were randomized to receive treatment. All data from site [REDACTED] (2 patients randomized to the ESA treatment group) are excluded due to Good Clinical Practice (GCP) violations; therefore a total of 836 patients were considered randomized for analysis: 415 to the roxadustat treatment group and 421 to ESA. Of the 836 patients randomized, 321 patients had previously received darbepoetin alfa and were randomized to the roxadustat vs darbepoetin alfa subgroup (158 to roxadustat, 163 to darbepoetin alfa) and 515 patients had previously received epoetin to the roxadustat vs epoetin alfa treatment subgroup (257 to roxadustat, 258 to epoetin alfa).

### Diagnosis and Main Criteria for Inclusion:

Male or female patients aged  $\geq 18$  years who were on stable HD, hemodiafiltration (HDF) or PD for anemia who met the inclusion criteria and did not meet the exclusion criteria were eligible to enter the study. The patients were to have received the same mode of dialysis for  $\geq 4$  months prior to randomization and who have received treatment with intravenous or subcutaneous epoetin or darbepoetin alfa treatment for  $\geq 8$  weeks prior to randomization, with stable weekly doses during 4 weeks prior to randomization. The mean of the patient's 3 most recent Hb values, as measured by central laboratory, during the screening period, obtained at least 4 days apart, were to be  $\geq 9.5$  g/dL and  $\leq 12.0$  g/dL with an absolute difference  $\leq 1.3$  g/dL between the highest and the lowest value.

**Test Product, Dose and Mode of Administration, Batch Numbers:** Roxadustat was supplied as red, film-coated, oval tablets for oral administration, in strengths of 20, 50 and 100 mg. The initial study drug dose was determined by the patient's average weekly dose of epoetin or darbepoetin alfa within 4 weeks prior to randomization [Table 1]. Dose adjustment of roxadustat according to the rules provided in [Table 3] was aimed at keeping patients' Hb levels between 10.0 to 12.0 g/dL and was based upon current Hb (assessed with the HemoCue® point-of-care device at the investigational site) and change in Hb over the preceding 4 weeks.

Batch numbers are provided in [Appendix 13.1.6].

**Table 3 Dose Adjustment Rules for Roxadustat**

Change in Hb Over Past 4 Weeks (g/dL) <sup>†</sup>	Hb (g/dL)		
	< 10.5	10.5 to < 12.0	12.0 to < 13.0
< -1.0	↑	↑	No change
-1.0 to 1.0	↑	No change	↓
> 1.0	No change	↓	↓

Hb: hemoglobin.

<sup>†</sup> Subtract first Hb value from last value Hb to calculate the change

- All dose adjustments were made based on Hb values using HemoCue, a point-of-care device.
- Dose increases by 1 dose step (↑) and reductions by 1 dose step (↓) were pre-set.
- If the dose adjustment was 'No change' per the above table, the dose remained unchanged and the next dose adjustment review was 4 weeks after that visit.
- The dose steps for roxadustat were as follows: 20, 40, 50, 70, 100, 150, 200, 250, 300, and 400 mg.
- The maximum dose was the dose step corresponding to 3.0 mg/kg (based on postdialysis weight in HD patients and in PD patients' weight minus abdominal fluid based on last filling) per administration or 400 mg, whichever was lower. At study visits where weight was collected the default weight and maximum allowed dose step for a patient was adjusted if the weight change was  $\geq 5\%$  compared to the previous default weight collected in the study. Initial default weight was weight at randomization visit.

- If there was a safety concern, investigators could deviate from the dose adjustment rules for roxadustat. This had to be discussed with the Medical Monitor and documented in the source documentation.
- The Medical Monitor was to be contacted if dose adjustments would lead to doses outside the limits of the dose step range; i.e., lower than 20 mg or higher than 400 mg.

In the following cases dose adjustments were made at any time outside the 4-weekly interval:

- Dose reduction in case of Hb rate of rise  $> 2$  g/dL within 4 weeks.
- Dose increase by 1 step in case the patient's Hb  $< 9.0$  g/dL (HemoCue) and no dose adjustment occurred in the preceding 4 weeks.

**At any time when Hb  $\geq 13.0$  g/dL**

- Stop dosing.
- Resume dosing when Hb  $< 12.0$  g/dL at a dose that was reduced by 2 steps.
- Next dose adjustment review was 4 weeks after dose resumption and in 4-weekly intervals thereafter.

**Dose Adjustment for Hb Rate of Rise  $> 2$  g/dL within 4 Weeks**

At any time during the Treatment Period if Hb increased by  $> 2.0$  g/dL at any time within 4 weeks, the dose was to be reduced by 1 dose step.

**Duration of Treatment:** Patients were treated for at least 52 weeks and continued taking treatment as assigned until a maximum of 104 weeks.

**Reference Product, Dose and Mode of Administration:**

Epoetin alfa (Eprex®) was supplied as a solution for subcutaneous or intravenous injection in a pre-filled syringe. It was centrally provided by a Contract Research Organization (CRO) in the following strengths: 1000, 2000, 3000, 4000, 6000 and 8000 IU, and was administered according to the US Prescribing Information (PI) or UK Summary of Product Characteristics (SmPC) of Eprex. Each pre-filled syringe was packaged in a single box. Each box had a unique kit number.

Darbepoetin alfa (Aranesp®) was supplied as a solution for subcutaneous or intravenous injection in a pre-filled syringe. It was centrally provided by a CRO in the following strengths: 10, 20, 30, 40, 60 and 100 µg, and was administered according to the USPI or EU SmPC of Aranesp. Each pre-filled syringe was packaged in a single box. Each box had a unique kit number.

**Criteria for Evaluation:**

*Efficacy:* There were 2 separate regionally based primary efficacy endpoints in this study, depending upon whether the data are being filed to support submission to the US FDA or to Ex-US health authorities, such as the EMA.

The EU (EMA) primary efficacy endpoint was change in Hb from baseline to the average level during the evaluation period (defined as week 28 until week 36), without having received rescue therapy (i.e., red blood cell [RBC] transfusion for all patients or ESA for

patients treated with roxadustat) within 6 weeks prior to and during this 8-week evaluation period.

The US (FDA) primary efficacy endpoint was change in Hb from baseline to the average level during the evaluation period (defined as week 28 until week 52), regardless of rescue therapy.

The key secondary efficacy endpoints were:

- Hb response, defined as mean Hb during weeks 28 to 36 within the target range of 10.0 to 12.0 g/dL without having received rescue therapy within 6 weeks prior to and during this 8 week evaluation period.
- Change from baseline in low density lipoprotein (LDL) cholesterol to the average LDL cholesterol of weeks 12 to 28.
- Mean monthly intravenous iron use (mg) during day 1 to week 36 (monthly defined as a period of 4 weeks).
- Change from baseline in the Short Form-36 questionnaire (SF-36) physical functioning (PF) subscore to the average PF subscore of weeks 12 to 28.
- Change from baseline in SF-36 Vitality (VT) subscore to the average VT subscore of weeks 12 to 28.
- Blood pressure effect: Change in mean arterial pressure (MAP) from baseline to the average MAP of weeks 20 to 28 and time to an increase in blood pressure during weeks 1 to 36.

*Safety:* Safety variables were:

- Treatment-emergent adverse events (TEAEs; frequency, severity, seriousness, and relationship to study drug), and pre-specified adjudicated cardiovascular and cerebrovascular events (reported separately),
- Vital signs (systolic and diastolic blood pressure, heart rate, and respiratory rate),
- Clinical laboratory variables (hematology, biochemistry including liver enzymes and total bilirubin, and urinalysis),
- Physical examination,
- 12-lead electrocardiogram (ECG),
- Vascular Access Thrombosis (VAT).

### **Statistical Methods:**

All statistical comparisons were made using 2-sided tests at  $\alpha = 0.05$  significance level unless specifically stated otherwise. Null hypotheses for superiority testing were of 'no treatment difference' and the corresponding alternative hypothesis was 2-sided. Null hypotheses for noninferiority testing were of inferiority of roxadustat treatment and were 1-sided at  $\alpha = 0.025$ . All data processing, summarization, and analyses were performed using SAS® Version 9.3 (SAS Enterprise Guide 4.3) or higher. All data were summarized by treatment arm (roxadustat and ESA), type of ESA treatment (darbepoetin alfa and epoetin alfa) and for the total, unless specified otherwise. For all results split by type of ESA treatment, previous ESA treatment before randomization was separated in 2 categories

(darbepoetin alfa or epoetin), unless specified otherwise. For continuous variables that were recorded as “< X” or “> X”, the value of “X” was used in the calculation of summary statistics. The original values were used for the listings. All percentages were rounded to 1 decimal place and lined up by the decimal place. The percentage was suppressed when the count was zero. For continuous variables, descriptive statistics included the number of patients (n), mean, SD, median, minimum and maximum. Frequencies and percentages were displayed for categorical data. Percentages by categories were based on the number of patients with no missing data, i.e., add up to 100%. Number of missing values is shown in the frequency tables. All data included in summary tables, inferential analyses or figures are also listed. Listings were done on all randomized patients and all assessments (all collected data in the eCRF were listed except the physical examination data). Pre-dialysis vital signs including blood pressure measurements were used, unless otherwise specified. For the safety analysis set population analyses, the actual treatment was used. For all other analysis populations, the planned treatment was used.

#### *Efficacy Analysis – Primary Efficacy Variable for the EU (EMA)*

The EU (EMA) primary efficacy endpoint was change in Hb from baseline to the average Hb of weeks 28 and 36, without having received rescue therapy (i.e., RBC transfusion for all patients or ESA for patients treated with roxadustat) within 6 weeks prior to and during this 8-week evaluation period. The primary EU (EMA) efficacy endpoint was analyzed using the per-protocol set.

For the average in weeks 28 to 36, all available Hb values obtained from the central laboratory were used (both scheduled and unscheduled). For patients who did not have an available Hb value during the week 28 to 36 period, imputation rules were applied.

In the event a patient received rescue therapy within 6 weeks prior to the week 28 to 36 period (i.e., in weeks 22 to 36), the Hb value was set to missing for 6 weeks after they stopped rescue and was imputed.

The EU primary efficacy endpoint was analyzed using a Mixed Model of Repeated Measures method adjusting for stratification factors, comparing roxadustat to ESA. After fitting the data, a computation statement was added to the model to calculate the average Hb values estimate during the period under consideration.

#### *Efficacy Analysis – Primary Efficacy Variable for the US (FDA)*

The US (FDA) primary efficacy endpoint was change in Hb from baseline to the average level of weeks 28 to week 52, regardless of rescue therapy. The US (FDA) primary efficacy endpoint was analyzed using the all randomized population.

For the average in weeks 28 to 52, all available Hb values obtained from the central laboratory were used (i.e., both scheduled and unscheduled Hb values).

For the analyses that required an Hb value by visit, the last available Hb value in the visit window was kept.

In case a patient did not have any available Hb value during the week 28 to 52 period (because they died or withdrew from the study for example), imputation rules were applied.

The US primary efficacy endpoint was computed from an analysis of covariance model with multiple imputation, adjusting for covariates

#### *Analysis of Secondary Efficacy Variables*

The key secondary efficacy endpoints in this study were tested in a fixed testing sequence [Table 4]

**Table 4 Key Secondary Efficacy Endpoints**

1	Hb response, defined as mean Hb during weeks 28 to 36 within the target range of 10.0 to 12.0 g/dL without having received rescue therapy within 6 weeks prior to and during this 8-week evaluation period.
2	Change from BL in LDL cholesterol to the average LDL cholesterol of weeks 12 to 28.
3	Mean monthly intravenous iron use (mg) during day 1 to week 36 (monthly defined as a period of 4 weeks).
4	Change from BL in SF-36 PF subscore to the average PF subscore of weeks 12 to 28.
5	Change from BL in SF-36 VT subscore to the average VT subscore of weeks 12 to 28.
6	Change from BL in MAP to the average MAP value of weeks 20 to 28.
7	Time to first occurrence of an increase in blood pressure: An increase from BL of $\geq 20$ mmHg SBP and SBP $\geq 170$ mmHg or an increase from BL of $\geq 15$ mmHg DBP and DBP $\geq 100$ mmHg during weeks 1 to 36.

BL: baseline; DBP: diastolic blood pressure; Hb: hemoglobin; LDL: low density lipoprotein; MAP: mean arterial pressure; PF: physical functioning; SBP: systolic blood pressure; SF-36: Short Form 36 questionnaire; VT: vitality

*Analysis of Safety Variables:* All safety data were summarized by treatment arm (roxadustat and ESA) and by previous ESA treatment (darbepoetin alfa and epoetin). Safety was assessed by evaluation of TEAEs, vital signs, clinical laboratory variables, physical examination, 12-lead ECG and VAT.

#### **Summary of Results/Conclusions:**

**Patient Disposition:** A total of 1081 patients signed the informed consent form and were screened, of these patients, 838 were randomized to receive treatment. All data from site [REDACTED] (2 patients randomized to the ESA treatment group) are excluded due to GCP violations; therefore a total of 836 patients were considered randomized for analysis.

Patients were enrolled under 3 protocol versions. A total of 379 patients in the All Randomized group (183 to the roxadustat treatment group, 196 to ESA) were enrolled after protocol amendment 1 (protocol v2.0).

A total of 558 (66.7%) patients completed the study up to 2 years of treatment, 249 (60.0%) in the roxadustat treatment group and 309 (73.4%) in the ESA treatment group [Figure 1].

Overall, 40.0% of patients in the roxadustat treatment group and 26.6% of patients in the ESA treatment group discontinued treatment up to 2 years. A total of 13.0% of patients withdrew due to death (14.9% roxadustat vs 11.2% ESA) and 9.1% withdrew by patient (12.0% vs 6.2%).



Premature withdrawal from the study overall during the first 2 years of treatment was higher in the roxadustat treatment group (28.4% of patients) compared with the ESA treatment group (21.9%); the most common reason for withdrawal from both treatment groups was death (16.4% vs 13.3%).

The greater number of discontinuations may be due to the open-label design of the study, as higher discontinuations in investigational drug groups are commonly higher than those seen with an active comparator considered standard of care.

Discontinuation was comparable overall between both subgroups of patients previously treated with darbepoetin alfa or epoetin: 33.6% of patients in the subgroup of patients previously treated with darbepoetin alfa and 33.0% in the subgroup of patients previously treated with epoetin discontinued treatment up to 2 years.

### **Demographics:**

Baseline demographics were comparable between the roxadustat and ESA treatment groups, the majority of patients were White (97.4%) and were randomized in Central and Eastern Europe (78.9%) [Table 5]. Imbalances between treatment groups included randomization in Bulgaria (16.7% of patients to roxadustat, 20.7% to ESA) and Serbia (12.3% vs 8.3%). Both treatment groups contained approximately 40% female patients, and 46% of patients were  $\geq 65$  years of age and were on stable dialysis receiving low doses of ESA.

Baseline demographics in the roxadustat vs darbepoetin alfa and roxadustat vs epoetin alfa treatment groups were comparable with the overall population; however, there was a greater proportion of patients in the subgroup of patients previously treated with darbepoetin alfa randomized in Croatia, Poland and Serbia compared with the subgroup of patients previously treated with epoetin (9.7% vs 5.5%, 7.2% vs 1.2% and 15.9% vs 6.8%, respectively) and a lower proportion of patients in the in the subgroup of patients previously treated with darbepoetin alfa randomized in Bulgaria, Romania and Russian Federation (13.4% vs 22.0%, 0.3% vs 7.6% and 8.1% vs 14.0%, respectively).

### **Efficacy Results:**

There were 2 separate regionally based primary efficacy endpoints in this study.

The study met both primary efficacy endpoints, demonstrating noninferiority of roxadustat to ESA treatments in terms of maintaining Hb levels in stable dialysis patients who had previously received ESA.

The difference in least-square mean (LSM) change in Hb from baseline to the average Hb of weeks 28 to 36 without rescue therapy (LSM difference 0.235 [95% CI: 0.132, 0.339]) and the average of weeks 28 to 52 (LSM difference 0.171 [0.082, 0.261]) regardless of rescue therapy for patients in the roxadustat group was noninferior to patients in the ESA treatment group ( $P < 0.001$  for noninferiority).

All sensitivity analyses, including the pre-planned EU subset analysis of patients with average epoetin  $\leq 200$  IU/kg or darbepoetin alfa  $\leq 1$   $\mu\text{g/kg}$  within the last 4 weeks prior to randomization, supported the main analysis.

Analysis of roxadustat versus darbepoetin alfa and versus epoetin alfa in patients previously treated with darbepoetin alfa and epoetin respectively, and the majority of subgroup analyses of the primary efficacy endpoints were also consistent with main analyses.

For the key secondary endpoints, superiority was demonstrated for LDL change from baseline (an approximate 15% decrease was seen in LDL cholesterol in the roxadustat treatment group compared with less than 5% in the ESA group) and use of intravenous iron (30% fewer patients in the roxadustat treatment group required intravenous iron); noninferiority was demonstrated for Hb response rate, MAP, time to first occurrence of hypertension and changes from baseline in SF36 PF and SF-36 VT subscores [Table 6].

Roxadustat and the ESA treatment were comparable in the requirement for, and risks of, hospitalization and effects on blood pressure overall, and for the majority of patient reported quality of life measurements where no notable change was seen from baseline, glycated hemoglobin (HbA1c) and C-reactive protein levels.

### **Safety Results:**

Median treatment duration was comparable in the roxadustat treatment group compared with the ESA treatment group; however, mean treatment duration and overall patient event years (PEY) in the safety emergent period were lower, largely due to increased patient withdrawals from the roxadustat group. A greater proportion of patients in the roxadustat treatment group withdrew from the study – most commonly due to deaths, and withdrawal by patient; differences were apparently driven by greater discontinuations in the roxadustat treatment subgroup vs the epoetin alfa treatment subgroup.

The majority of TEAEs in both treatment groups were non-serious, mild to moderate in severity and considered unrelated to treatment by the investigator.

The overall incidence of TEAEs and TEAEs PEY during the safety emergent period was comparable between treatment groups, with the overall event profile largely driven by events in the Infections and Infestations (most commonly viral upper respiratory tract infections and bronchitis in both treatment groups), Injury, Poisoning and Procedural Complications (with a greater incidence of arteriovenous (AV) fistula thrombosis in the roxadustat treatment group, mainly in the subgroup of patients receiving roxadustat compared with epoetin), Vascular Disorders (most commonly hypertension in both treatment groups) and Gastrointestinal Disorders (with a greater incidence of diarrhea and nausea in the roxadustat treatment group) MedDRA SOCs [Table 7].

TEAEs with an increased incidence in the roxadustat treatment group were mostly in the Gastrointestinal Disorders, Skin and Subcutaneous Disorders, Nervous System Disorders and General Disorders and Administration Site Conditions SOCs. The majority of these were considered mild or moderate in severity and were nonserious.

There were imbalances in the overall incidence of nausea and arteriovenous fistula thrombosis, with a greater number in the roxadustat treatment group, and upper respiratory tract/viral upper respiratory tract infections, iron deficiency and muscle spasms occurring in a greater number of patients in the ESA treatment group. Hypertension and hypotension were

seen in both treatment groups in comparable amounts. There was no notable difference between treatment groups in the profile of TEAEs associated with the drug-drug interaction of roxadustat with statins.

The safety profiles seen in the subgroup of patients previously treated with darbepoetin alfa was generally comparable with the overall population; however, in the roxadustat vs epoetin alfa treatment subgroups the safety profile appeared favorable towards epoetin alfa.

The incidence of TEAEs leading to withdrawal was higher in the roxadustat treatment group compared with the ESA treatment group, with hazard ratios favoring the ESA treatment group; there was an increased incidence of serious TEAEs and TEAEs leading to patient death in the roxadustat treatment group. The cumulative incidence of serious TEAEs and deaths over time was greater in the roxadustat treatment group compared with the ESA treatment group. Differences were apparently due to the increased incidences of deaths and serious TEAEs over time in patients receiving roxadustat compared with epoetin alfa.

There was a greater proportion of deaths in the roxadustat treatment group compared with the ESA group; however, baseline disease factors associated with mortality (including age, cardiovascular history and diabetes) did not appear to affect mortality or account for the mortality difference seen between treatment groups.

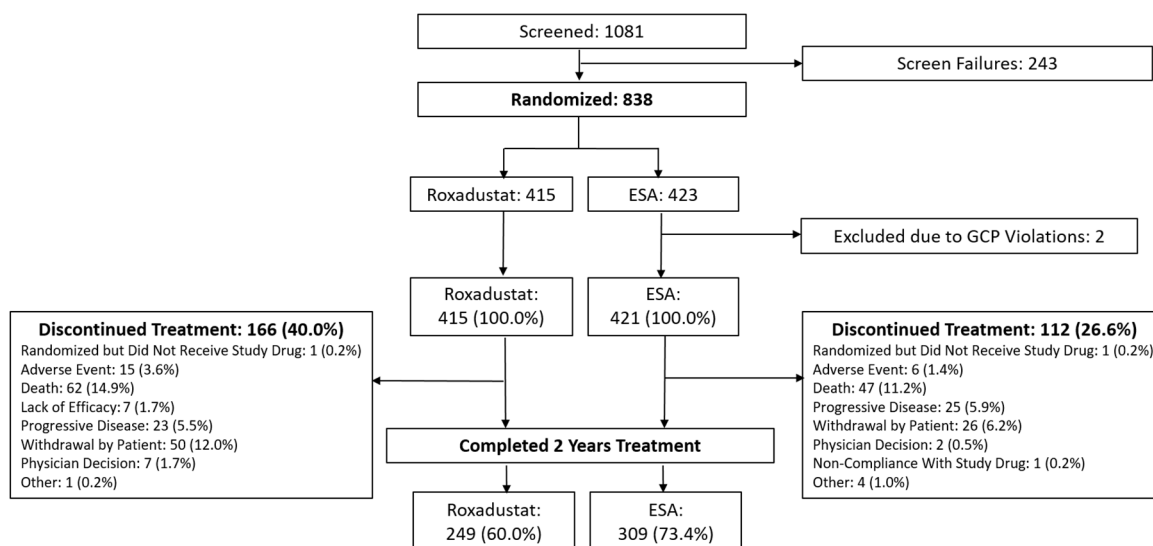
The incidence of potentially clinically significant liver function and laboratory assessments was comparable between the 2 treatment groups. There was a greater proportion of patients in the roxadustat treatment group who recorded with alanine aminotransferase and/or aspartate aminotransferase  $> 3 \times$  upper limit of normal (ULN) and/or total bilirubin  $> 2 \times$  ULN; however, these changes were transient and returned to baseline levels over time. No Hy's law cases were observed during this study.

## CONCLUSIONS:

- The study met its primary objective and demonstrated noninferiority of roxadustat to ESA treatment in terms of maintaining Hb levels in stable dialysis patients converted from ESA.
- Comparisons of roxadustat with darbepoetin and epoetin alfa also demonstrated noninferiority.
- Roxadustat was superior to ESA treatment in change in LDL cholesterol from baseline and use of intravenous iron.
- Noninferiority was demonstrated for Hb response rate, MAP, time to first occurrence of hypertension and changes from baseline in SF-36 PF and SF-36 VT subscores.
- There were imbalances in the occurrence of serious TEAEs, TEAEs leading to patient death and TEAEs leading to withdrawal over time, with hazard ratios favoring ESA treatment. There was no apparent cause of the imbalance in incidence of overall mortality, and cardiovascular-related mortality between treatment groups.
- Differences in the safety profile appear driven by the comparison of roxadustat with epoetin alfa rather than with darbepoetin alfa, most notably the apparent imbalance in the number of patient deaths between treatment groups in the epoetin alfa subgroup.

**Date of Report:** 11 Oct 2019

**Figure 1 Patient Disposition Flowchart**



ESA: erythropoiesis-stimulating agent; GCP: Good Clinical Practice

Source: End-of-text Table 12.1.1.1, End-of-text Table 12.1.1.2, End-of-text Table 12.1.1.3.1, End-of-text Table 12.1.1.6.

**Table 5 Summary of Demographics (Overall Population; Safety Analysis Set)**

Parameter	Category/Statistic	Roxadustat (n = 414)	ESA (n = 420)	Total (n = 834)
Sex	Male	245 (59.2%)	235 (56.0%)	480 (57.6%)
	Female	169 (40.8%)	185 (44.0%)	354 (42.4%)
Age (years)	n	414	420	834
	Mean (SD)	61.0 (13.8)	61.8 (13.4)	61.4 (13.6)
	Median	62.5	63.0	63.0
	Min, Max	24, 91	27, 91	24, 91
Age (years)	< 65	222 (53.6%)	229 (54.5%)	451 (54.1%)
	65 to 74	114 (27.5%)	115 (27.4%)	229 (27.5%)
	≥ 75	78 (18.8%)	76 (18.1%)	154 (18.5%)
Race	White	405 (97.8%)	407 (96.9%)	812 (97.4%)
	Black or African American	6 (1.4%)	6 (1.4%)	12 (1.4%)
	Asian	1 (0.2%)	3 (0.7%)	4 (0.5%)
	Other	2 (0.5%)	4 (1.0%)	6 (0.7%)
Height (cm)	n	413	419	832
	Mean (SD)	168.28 (8.80)	168.06 (9.06)	168.17 (8.93)
	Median	168.00	168.00	168.00
	Min, Max	144.0, 190.0	147.0, 198.0	144.0, 198.0
Weight (kg)	n	414	420	834
	Mean (SD)	76.29 (15.88)	76.18 (17.25)	76.23 (16.58)
	Median	75.00	74.05	74.35
	Min, Max	45.5, 144.0	45.4, 155.4	45.4, 155.4
BMI (kg/m <sup>2</sup> )	n	413	419	832
	Mean (SD)	26.87 (4.86)	26.95 (5.59)	26.91 (5.24)
	Median	26.23	26.08	26.15
	Min, Max	16.1, 46.0	16.5, 52.5	16.1, 52.5
Region	Western Europe	86 (20.8%)	90 (21.4%)	176 (21.1%)
	Central and Eastern Europe	328 (79.2%)	330 (78.6%)	658 (78.9%)

Table continued on next page

Parameter	Category/Statistic	Roxadustat (n = 414)	ESA (n = 420)	Total (n = 834)
Country	Belgium	11 (2.7%)	20 (4.8%)	31 (3.7%)
	Bulgaria	69 (16.7%)	87 (20.7%)	156 (18.7%)
	Croatia	28 (6.8%)	31 (7.4%)	59 (7.1%)
	Czech Republic	10 (2.4%)	6 (1.4%)	16 (1.9%)
	France	5 (1.2%)	7 (1.7%)	12 (1.4%)
	Georgia (Republic)	2 (0.5%)	4 (1.0%)	6 (0.7%)
	Germany	15 (3.6%)	19 (4.5%)	34 (4.1%)
	Hungary	63 (15.2%)	73 (17.4%)	136 (16.3%)
	Italy	19 (4.6%)	20 (4.8%)	39 (4.7%)
	Poland	18 (4.3%)	11 (2.6%)	29 (3.5%)
	Portugal	11 (2.7%)	6 (1.4%)	17 (2.0%)
	Romania	20 (4.8%)	20 (4.8%)	40 (4.8%)
	Russian Federation	52 (12.6%)	46 (11.0%)	98 (11.8%)
	Serbia	51 (12.3%)	35 (8.3%)	86 (10.3%)
	Slovakia	15 (3.6%)	17 (4.0%)	32 (3.8%)
	Spain	17 (4.1%)	12 (2.9%)	29 (3.5%)
	United Kingdom	8 (1.9%)	6 (1.4%)	14 (1.7%)

BMI: body mass index (weight [kg]/height [m<sup>2</sup>]); ESA: erythropoiesis-stimulating agent; Max: maximum; Min: minimum

Source: End-of-text Table 12.1.2.1.2

**Table 6 Summary of Primary and Key Secondary Endpoints**

Endpoint	Roxadustat	ESA	Result
<b>Primary EU (EMA): Change from BL to the Average Hb (g/dL) in Weeks 28 to 36 without Rescue Therapy</b>			
Roxadustat vs ESA treatment	PPS: n = 386 LSM (95% CI): 0.428 (0.350, 0.506)	PPS: n = 397 LSM (95% CI): 0.193 (0.117, 0.268)	LSM Difference (95% CI): 0.235 (0.132, 0.339) P < 0.001 † P < 0.001 ‡
Roxadustat vs darbepoetin alfa	PPS: n = 147 LSM (95% CI): 0.493 (0.370, 0.616)	PPS: n = 153 LSM (95% CI): 0.318 (0.199, 0.436)	LSM Difference (95% CI): 0.175 (0.013, 0.337) P < 0.001 † P = 0.034 ‡
Roxadustat vs epoetin alfa	PPS: n = 239 LSM (95% CI): 0.409 (0.308, 0.509)	PPS: n = 244 LSM (95% CI): 0.140 (0.043, 0.238)	LSM Difference (95% CI): 0.268 (0.134, 0.403) P < 0.001 † P < 0.001 ‡
<b>Primary US (FDA): Change from BL to the Average Hb (g/dL) in Weeks 28 to 52 Regardless Use of Rescue Therapy</b>			
Roxadustat vs ESA treatment	All randomized: n = 415 LSM (95% CI): 0.363 (0.288, 0.438)	All randomized: n = 421 LSM (95% CI): 0.192 (0.121, 0.262)	LSM Difference (95% CI): 0.171 (0.082, 0.261) P < 0.001 † P < 0.001 ‡
Roxadustat vs darbepoetin alfa	All randomized: n = 158 LSM (95% CI): 0.504 (0.392, 0.617)	All randomized: n = 163 LSM (95% CI): 0.349 (0.244, 0.455)	LSM Difference (95% CI): 0.155 (0.021, 0.290) P < 0.001 † P = 0.024 ‡
Roxadustat vs epoetin alfa	All randomized: n = 257 LSM (95% CI): 0.265 (0.168, 0.362)	All randomized: n = 258 LSM (95% CI): 0.081 (-0.010, 0.172)	LSM Difference (95% CI): 0.184 (0.066, 0.301) P < 0.001 † P = 0.002 ‡
<i>Table continued on next page</i>			

Endpoint	Roxadustat	ESA	Result
<b>Key Secondary Endpoints</b>			
Hb response during weeks 28 to 36 without rescue therapy	PPS: n = 386 Number of Responders: 325 (84.2%)	PPS: n = 397 Number of Responders: 327 (82.4%)	Difference of proportions (95% CI): 2.3% (-2.9%, 7.6%) §
Change from baseline in LDL cholesterol (mmol/L) to average in weeks 12 to 28 regardless of fasting status	FAS: n = 413 LSM (95% CI): -0.459 (-0.517, -0.401)	FAS: n = 420 LSM (95% CI): -0.082 (-0.138, -0.026)	LSM Difference (95% CI): -0.377 (-0.451, -0.304) P < 0.001 ¶
Mean monthly use of intravenous iron (mg) from day 1 to week 36	FAS: n = 413 LSM (95% CI): 21.6 (14.0, 29.3)	FAS: n = 420 LSM (95% CI): 53.5 (46.0, 61.1)	LSM Difference (95% CI): -31.9 (-41.4, -22.4) P < 0.001 ¶
Change from BL in SF-36 PF subscore in weeks 12 to 28	PPS: n = 386 LSM (95% CI): 0.050 (-0.640, 0.740)	PPS: n = 397 LSM (95% CI): -0.155 (-0.825, 0.514)	LSM Difference (95% CI): 0.205 (-0.649, 1.059) ††
Change from BL in SF-36 VT subscore in weeks 12 to 28	PPS: n = 386 LSM (95% CI): 0.460 (-0.329, 1.249)	PPS: n = 397 LSM (95% CI): -0.396 (-1.165, 0.373)	LSM Difference (95% CI): 0.856 (-0.115, 1.828) ††
Change from BL in MAP (mmHg) in weeks 20 to 28	PPS: n = 386 LSM (95% CI): -0.969 (-1.838, -0.099)	PPS: n = 397 LSM (95% CI): -0.120 (-0.972, 0.732)	LSM Difference (95% CI): -0.849 (-1.971, 0.273) ‡‡
Time to first increase in BP (incidence per 100 patient years at risk)	PPS: n = 386 32.2	PPS: n = 397 35.7	Hazard Ratio: 0.924 (0.669, 1.276) §§
Change from BL in MAP (mmHg) in weeks 20 to 28	FAS: n = 413 LSM (95% CI): -0.739 (-1.600, 0.123)	FAS: n = 420 LSM (95% CI): -0.0160 (-0.997, 0.678)	LSM Difference (95% CI): 0.579 (-1.694, 0.536) P = 0.308 ‡
Time to first increase in BP (incidence per 100 patient years at risk)	FAS: n = 413 32.8	FAS: n = 420 37.2	Hazard Ratio: 0.915 (0.668, 1.254) P = 0.582 ‡

† 1-sided P value (noninferiority); adjusted margin for noninferiority: -0.75.

‡ 2-sided P value (superiority)

§ Margin for noninferiority: -15%

¶ P value for superiority

†† Margin for noninferiority: -3

‡‡ Margin for noninferiority: 1

§§ Margin for noninferiority: 1.3

BL: baseline; BP: blood pressure; CI: confidence interval; ESA: erythropoiesis-stimulating agent; Hb: hemoglobin; FAS: full analysis set; LDL: low density lipoprotein; LSM: least squares mean; MAP: mean arterial pressure; PF: physical functioning; PPS: per protocol set; SF-36: Short Form-36 questionnaire; VT: vitality.

Source: End-of-Text Table 12.3.1.1.2.1, End-of-Text Table 12.3.1.2.2.1, End-of-Text Table 12.3.2.1, End-of-Text Table 12.3.2.2.2, Table 12.3.2.3.2, End-of-Text Table 12.3.2.4.2, End-of-Text Table 12.3.2.5.1.3, End-of-Text Table 12.3.2.6.1.3, End-of-Text Table 12.3.2.7.2, End-of-Text Table 12.3.2.7.3, End-of-Text Table 12.3.2.8.1.1, End-of-Text Table 12.3.2.8.1.2

**Table 7 Common ( $\geq 5\%$  Patients in any Treatment Group) Treatment-Emergent Adverse Event during the Safety Emergent Period (Safety Analysis Set)**

MedDRA v20.0 Preferred Term	Roxadustat (n=414; PEY=662.2)		ESA (n=420; PEY=752.2)	
	n (%)	#E (Event rate/100 PEY)	n (%)	#E (Event rate/100 PEY)
<b>Overall</b>	<b>359 (86.7%)</b>	<b>2454 (370.6)</b>	<b>361 (86.0%)</b>	<b>2625 (349.0)</b>
Hypertension	74 (17.9%)	111 (16.8)	79 (18.8%)	121 (16.1)
Arteriovenous fistula thrombosis	50 (12.1%)	71 (10.7)	31 (7.4%)	39 (5.2)
Headache	36 (8.7%)	41 (6.2)	29 (6.9%)	39 (5.2)
Diarrhoea	35 (8.5%)	53 (8.0)	35 (8.3%)	64 (8.5)
Bronchitis	33 (8.0%)	43 (6.5)	29 (6.9%)	37 (4.9)
Hypotension	33 (8.0%)	45 (6.8)	27 (6.4%)	43 (5.7)
Iron deficiency	30 (7.2%)	39 (5.9)	51 (12.1%)	64 (8.5)
Nausea	29 (7.0%)	31 (4.7)	8 (1.9%)	10 (1.3)
Viral upper respiratory tract infection	29 (7.0%)	62 (9.4)	39 (9.3%)	68 (9.0)
Pneumonia	23 (5.6%)	27 (4.1)	27 (6.4%)	30 (4.0)
Arteriovenous fistula site complication	23 (5.6%)	38 (5.7)	21 (5.0%)	31 (4.1)
Hyperparathyroidism secondary	22 (5.3%)	24 (3.6)	16 (3.8%)	17 (2.3)
Anaemia	21 (5.1%)	27 (4.1)	16 (3.8%)	21 (2.8)
Atrial fibrillation	20 (4.8%)	27 (4.1)	25 (6.0%)	27 (3.6)
Muscle spasms	15 (3.6%)	21 (3.2)	33 (7.9%)	48 (6.4)
Upper respiratory tract infection	14 (3.4%)	20 (3.0)	22 (5.2%)	30 (4.0)
Fall	13 (3.1%)	13 (2.0)	21 (5.0%)	26 (3.5)

Event Rate per 100 PEY is defined as (number of events)\*100 divided by PEY during Safety Emergent Period.

Sorting order: incidence by Preferred Term in the roxadustat treatment group.

#E: number of events; ESA: erythropoiesis-stimulating agent; PEY: Patient Exposure Years; PT: preferred term

Source: End-of-text Table 12.6.1.2.1, End-of-text Table 12.6.1.13, End-of-text Table 12.6.1.23.1

**Table 8 Common ( $\geq 1\%$  Patients in Any Treatment Group) Serious Treatment-Emergent Adverse Event (MedDRA v20.0; Safety Analysis Set)**

MedDRA v20.0 System Organ Class Preferred Term	Roxadustat (n = 414; PEY = 662.2)		ESA (n = 420; PEY = 752.2)	
	n (%)	Event rate/100 PEY	n (%)	Event rate/100 PEY
<b>Overall</b>	<b>210 (50.7%)</b>	<b>539 (81.4)</b>	<b>189 (45.0%)</b>	<b>542 (72.1)</b>
<b>Infections and Infestations</b>	<b>82 (19.8%)</b>	<b>126 (19.0)</b>	<b>66 (15.7%)</b>	<b>95 (12.6)</b>
Pneumonia	15 (3.6%)	15 (2.3)	21 (5.0%)	22 (2.9)
Peritonitis	10 (2.4%)	15 (2.3)	3 (0.7%)	4 (0.5)
Sepsis	8 (1.9%)	8 (1.2)	9 (2.1%)	9 (1.2)
Bronchitis	5 (1.2%)	5 (0.8)	3 (0.7%)	3 (0.4)
Gangrene	5 (1.2%)	6 (0.9)	4 (1.0%)	7 (0.9)
Urinary tract infection	4 (1.0%)	4 (0.6)	0	0
Gastroenteritis	0	0	6 (1.4%)	6 (0.8)

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<b>MedDRA v20.0 System Organ Class Preferred Term</b>	<b>Roxadustat (n = 414; PEY = 662.2)</b>		<b>ESA (n = 420; PEY = 752.2)</b>	
	<b>n (%)</b>	<b>Event rate/100 PEY</b>	<b>n (%)</b>	<b>Event rate/100 PEY</b>
<b>Injury, Poisoning and Procedural Complications</b>	<b>58 (14.0%)</b>	<b>80 (12.1)</b>	<b>51 (12.1%)</b>	<b>79 (10.5)</b>
Arteriovenous fistula thrombosis	29 (7.0%)	37 (5.6)	15 (3.6%)	18 (2.4)
Arteriovenous fistula site complication	6 (1.4%)	7 (1.1)	5 (1.2%)	5 (0.7)
Femur fracture	2 (0.5%)	2 (0.3)	5 (1.2%)	5 (0.7)
Shunt thrombosis	1 (0.2%)	1 (0.2)	4 (1.0%)	5 (0.7)
Fall	0	0	6 (1.4%)	6 (0.8)
<b>Cardiac Disorders</b>	<b>57 (13.8%)</b>	<b>82 (12.4)</b>	<b>65 (15.5%)</b>	<b>102 (13.6)</b>
Atrial fibrillation	12 (2.9%)	14 (2.1)	8 (1.9%)	8 (1.1)
Acute myocardial infarction	9 (2.2%)	9 (1.4)	11 (2.6%)	13 (1.7)
Cardiac failure	8 (1.9%)	8 (1.2)	9 (2.1%)	9 (1.2)
Angina pectoris	5 (1.2%)	5 (0.8)	6 (1.4%)	8 (1.1)
Cardiac failure congestive	5 (1.2%)	5 (0.8)	1 (0.2%)	1 (0.1)
Cardiac arrest	4 (1.0%)	4 (0.6)	8 (1.9%)	9 (1.2)
Myocardial ischaemia	4 (1.0%)	5 (0.8)	4 (1.0%)	4 (0.5)
Myocardial infarction	1 (0.2%)	1 (0.2)	6 (1.4%)	6 (0.8)
Supraventricular tachycardia	1 (0.2%)	1 (0.2)	5 (1.2%)	5 (0.7)
<b>Vascular Disorders</b>	<b>35 (8.5%)</b>	<b>44 (6.6)</b>	<b>30 (7.1%)</b>	<b>51 (6.8)</b>
Hypertension	10 (2.4%)	10 (1.5)	5 (1.2%)	5 (0.7)
Deep vein thrombosis	4 (1.0%)	5 (0.8)	0	0
Hypotension	4 (1.0%)	5 (0.8)	1 (0.2%)	3 (0.4)
Peripheral arterial occlusive disease	2 (0.5%)	2 (0.3)	4 (1.0%)	4 (0.5)
Peripheral ischaemia	2 (0.5%)	2 (0.3)	4 (1.0%)	6 (0.8)
<b>Respiratory, Thoracic and Mediastinal Disorders</b>	<b>29 (7.0%)</b>	<b>35 (5.3)</b>	<b>21 (5.0%)</b>	<b>27 (3.6)</b>
Pleural effusion	6 (1.4%)	7 (1.1)	2 (0.5%)	3 (0.4)
Pulmonary oedema	6 (1.4%)	6 (0.9)	2 (0.5%)	2 (0.3)
Dyspnoea	4 (1.0%)	4 (0.6)	4 (1.0%)	4 (0.5)
Pulmonary embolism	4 (1.0%)	4 (0.6)	1 (0.2%)	1 (0.1)
<b>General Disorders and Administration Site Conditions</b>	<b>28 (6.8%)</b>	<b>34 (5.1)</b>	<b>20 (4.8%)</b>	<b>24 (3.2)</b>
Sudden death	7 (1.7%)	7 (1.1)	3 (0.7%)	3 (0.4)
Death	6 (1.4%)	6 (0.9)	3 (0.7%)	3 (0.4)
Pyrexia	4 (1.0%)	4 (0.6)	4 (1.0%)	5 (0.7)
<b>Gastrointestinal Disorders</b>	<b>23 (5.6%)</b>	<b>32 (4.8)</b>	<b>27 (6.4%)</b>	<b>42 (5.6)</b>
Duodenal ulcer	4 (1.0%)	4 (0.6)	0	0
Gastrointestinal haemorrhage	0	0	6 (1.4%)	6 (0.8)

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<b>MedDRA v20.0 System Organ Class Preferred Term</b>	<b>Roxadustat (n = 414; PEY = 662.2)</b>		<b>ESA (n = 420; PEY = 752.2)</b>	
	<b>n (%)</b>	<b>Event rate/100 PEY</b>	<b>n (%)</b>	<b>Event rate/100 PEY</b>
<b>Nervous System Disorders</b>	<b>15 (3.6%)</b>	<b>18 (2.7)</b>	<b>21 (5.0%)</b>	<b>28 (3.7)</b>
Cerebral infarction	0	0	4 (1.0%)	5 (0.7)
<b>Metabolism and Nutrition Disorders</b>	<b>12 (2.9%)</b>	<b>15 (2.3)</b>	<b>12 (2.9%)</b>	<b>13 (1.7)</b>
Hyperkalaemia	4 (1.0%)	4 (0.6)	3 (0.7%)	3 (0.4)
<b>Product Issues</b>	<b>6 (1.4%)</b>	<b>7 (1.1)</b>	<b>1 (0.2%)</b>	<b>1 (0.1)</b>
Device malfunction	4 (1.0%)	5 (0.8)	0	0
<b>Blood and Lymphatic System Disorders</b>	<b>5 (1.2%)</b>	<b>5 (0.8)</b>	<b>8 (1.9%)</b>	<b>9 (1.2)</b>
Anaemia	5 (1.2%)	5 (0.8)	7 (1.7%)	8 (1.1)

Event Rate per 100 PEY is defined as (number of events)\*100 divided by PEY during Safety Emergent Period.

SOCs are included in the table only when at least 1 PT within the SOC exceeded a threshold of 1.0%.

Sorting order: incidence by SOC, then incidence by PT.

#E: number of events; ESA: erythropoiesis-stimulating agent; PEY: Patient Exposure Years; PT: preferred term.

Source: End-of-text Table 12.6.1.6, End-of-text Table 12.6.1.23.2.