FDA Briefing Document

Cardiovascular and Renal Drugs Advisory Committee Meeting

July 15, 2021

Roxadustat

The committee will discuss the safety and efficacy of the New Drug Application (NDA) 213805 for roxadustat, an oral film-coated tablet submitted by FibroGen, Inc. The proposed indication is for the treatment of anemia due to chronic kidney disease (CKD) in adult patients not on dialysis and on dialysis.

Date Prepared: June 14, 2021

Division of Nonmalignant Hematology

and

Office of Cardiology, Hematology, Endocrinology, and Nephrology

Office of New Drugs

Center for Drug Development & Research

US Food & Drug Administration

Silver Spring, MD 20993

Department of Health & Human Services

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought roxadustat to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the Advisory Committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the Advisory Committee meeting.

Contents

Table of Tables

Table of Figures

List of Acronyms

AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BMI	body mass index
CI	confidence interval
CHF	congestive heart failure
CKD	chronic kidney disease
eGFR	estimated glomerular filtration rate
ESA	erythropoiesis-stimulating agent
ESRD	end stage renal disease
Hb	hemoglobin
HD	hemodialysis
HIF	hypoxia-inducible factor
HR	hazard ratio
LSM	least squares mean
MACE	major adverse cardiovascular events
MI	myocardial infarction
NI	non-inferiority
PHI	prolyl hydroxylase inhibitor
PD	peritoneal dialysis
P-Y	patient-year
RBC	red blood cell
SAE	serious adverse event
TBL	total bilirubin
TIW	three times weekly
ULN	upper limit of normal
US	United States

Introduction

This is the FDA briefing material for the July 15, 2021 meeting of the Cardiovascular and Renal Drugs Advisory Committee. The Committee will discuss the data in support of New Drug Application 213805 for roxadustat, to consider its benefits and risks for the applicant's proposed indication: "Roxadustat is indicated for the treatment of anemia due to chronic kidney disease (CKD) in adult patients not on dialysis and on dialysis."

Erythropoiesis stimulating agents (ESAs), such as epoetin alfa and darbepoetin alfa, are typically used in the treatment of the anemia of CKD, and they increase red blood cell (RBC) mass through the same mechanism as endogenous erythropoietin. Roxadustat is an orally administered reversible inhibitor of hypoxia inducible factor (HIF)-prolyl hydroxylases (PH). Inhibition of HIF-PH is thought to increase levels of endogenous erythropoietin, thereby increasing erythropoiesis. By avoiding supra-physiologic plasma levels of exogenous erythropoietin analogues, the applicant hypothesizes that there will be fewer undesirable effects, thus providing a safer alternative to ESAs. The applicant also believes that roxadustat has salutary effects on iron metabolism that will reduce the requirements for iron in these patients. If approved, roxadustat would represent the first drug in this class in the United States (US). Importantly, additional drugs in this class are in late-stage development, and may be submitted to FDA for evaluation.

The NDA includes an extensive database in support of roxadustat's efficacy and safety for both the NDD and DD populations. The development of roxadustat for the two populations proceeded concurrently; therefore, results of the DD studies were not available for the planning of the NDD studies, and vice versa.

For the NDD patient population, three similarly designed, adequate and well-controlled studies support roxadustat's efficacy for the treatment of anemia. These studies, referred to as anemia "correction" studies, enrolled patients with CKD who were anemic at baseline (mean hemoglobin [Hb] ~9 g/dL), and randomized them to roxadustat or placebo. A fourth study was unique—with randomization to roxadustat or darbepoetin alfa—and provides the ability to compare the efficacy and safety of roxadustat to an ESA in this population.

For the DD patient population, there were also three principal studies; these enrolled patients with CKD and incident or stable dialysis. At baseline, the mean Hb was slightly higher than in the studies in the NDD population, about 9.6 g/dL overall. These studies compared roxadustat to epoetin alfa. A unique study, considered separately, was conducted in Europe and permitted the use of two different ESAs (epoetin alfa or darbepoetin alfa). One of the ESAs (Eprex, epoetin alfa) is not licensed in the US and is not considered to be the same as US licensed Procrit/Epogen (epoetin alfa).

As is the case with ESAs, roxadustat is titrated to achieve a target Hb level, and roxadustat's efficacy is not in question. All studies in both the NDD and DD patient populations demonstrated efficacy. The principal issue before the Committee is the drug's safety, and safety with respect to the specific CKD patient populations.

During the development of drugs for the treatment of anemia of CKD, we have generally asked sponsors to demonstrate noninferiority (or superiority) with respect to major adverse cardiovascular events (MACE) for both the dialysis and non-dialysis populations (vs. an active comparator and placebo,

respectively). In this development program, MACE included the following events: all-cause mortality (ACM), non-fatal myocardial infarction (MI), and non-fatal stroke. (The MACE composite here differs slightly from the composite typically used in cardiovascular outcome trials; here all-cause mortality, rather than cardiovascular mortality, was used.) The applicant has provided these MACE assessments, as requested, and they represent an important part of this application.

Placebo-controlled studies in the NDD patient population enrolled subjects with significant anemia, and because anemia was less likely to improve in subjects who received placebo, they were more likely to discontinue from the study. Thus, for the three trials overall, completion rates were 62% and 41% in patients randomized to roxadustat and placebo, respectively. The difference in completion rates confounded a number of the safety analyses; in particular, the MACE results are sensitive to the duration of post-treatment observation.

Beyond MACE, a number of safety issues merit consideration and are described herein.

Roxadustat

As noted above, roxadustat is an orally administered reversible inhibitor of HIF- PH, intended to improve anemia in patients with CKD in both the NDD and DD populations.

Roxadustat is proposed to be available as a film-coated tablet for oral administration containing 20, 50, 70, 100, or 150 mg of roxadustat. The proposed recommended starting dose for patients on dialysis or patients who are not on dialysis and not on an ESA is 70 mg three times per week (TIW) in patients weighing <100 kg and 100 mg TIW in patients weighing ≥100 kg.

Roxadustat is not marketed in the US, but has marketing authorization in the People's Republic of China (December, 2018) and Japan (September, 2019). Both countries approved use first for the treatment of anemia due to CKD for patients on dialysis followed by an approval for patients not on dialysis. Based on the safety data submitted in this NDA, the People's Republic of China has updated the English language version of their label to include safety information for cardiovascular events, vascular access thrombosis, deep vein thrombosis, seizures, and serious infections. The English language version of the Japanese label has a Boxed Warning for serious thromboembolism including cerebral infarction, myocardial infarction (MI), and pulmonary embolism. Additional notable adverse reactions in the Japanese labeling are thromboembolism, including shunt occlusion, and seizures.

Anemia of Chronic Kidney Disease

Anemia is a common complication of CKD that develops early in the course of the disease and worsens as CKD progresses. The overall prevalence of CKD in the US adult population is estimated at 15%, with an estimated 17.2 million having Stages 3-5 CKD. The prevalence of anemia increases as the glomerular filtration rate (GFR) declines [1, 2]. It is estimated that 50% of patients with Stage 4 and 5 CKD not on dialysis and 90% of patients requiring dialysis are anemic. The etiology of anemia of CKD is multifactorial and includes erythropoietin deficiency, impaired ability to absorb iron (iron deficiency), inability to utilize stored iron (chronic disease), blood loss, and shortened RBC survival. Symptoms of anemia include fatigue, reduced exercise tolerance, and dyspnea.

Currently available therapeutic options for anemia of CKD include iron, ESAs, and RBC transfusions. Patients with CKD are routinely monitored for evidence of iron deficiency and treated with iron if deficient. Approximately 8% of patients with Stage 4 and 13% of patients with Stage 5 CKD receive an

ESA. Pre-end-stage renal disease use of an ESA in the adult population by age category ranges from approximately 12% to 17% [3]. Most patients with CKD receiving hemodialysis (HD) require ESAs to correct anemia and reduce the need for RBC transfusion and its attendant risks, including the risks of alloreactivity and rejection after kidney transplantation. In order to place roxadustat into proper context in the armamentarium of therapies for the anemia of CKD, some general background on ESAs is important.

Erythropoiesis Stimulating Agents

Epoetin alfa is a glycoprotein manufactured by recombinant DNA technology that contains the identical amino acid sequence of isolated natural erythropoietin and has the same biological effects as endogenous erythropoietin. ESAs bind to and activate the human erythropoietin receptor and stimulate red blood cell production in the bone marrow. ESA use for these indications has spanned over 30 years.

Currently marketed ESAs include epoetin alfa, darbepoetin alfa, methoxy polyethylene glycol-epoetin beta, and epoetin alfa-epbx. Dosing can vary from three times a week to monthly, depending on the specific agent and setting. All are administered by the intravenous or subcutaneous routes; none can be orally administered.

Table 1: US-Licensed ESAs for the Treatment of Anemia Due to Chronic Kidney Disease (CKD)

Product Names **Established (trade)**	**Approval Year**
epoetin alfa (Epogen/Procrit)	1989
darbepoetin alfa (Aranesp)	2001
methoxy polyethylene glycol-epoetin beta (Mircera)	2007
epoetin alfa-epbx (Retacrit)	2018

Subsequent to the initial approval of an ESA for patients with CKD in 1989, the ESA labeling has undergone significant revisions because of accumulating knowledge from safety surveillance and clinical trials. These labeling revisions have included the addition of a Boxed Warning for increased mortality, serious cardiovascular and thromboembolic events; warnings for hypertension, seizures, and thrombotic events including vascular access thrombosis; and in dosage and administration, a reduction in the recommended "target Hb," and a recommendation to discontinue the ESA in patients in whom Hb does not respond adequately over a 12-week escalation period. Other major adverse reactions of ESAs include thrombosis, hypertension, seizures, and pure red cell aplasia.

ESA use in patients with CKD can confer an increased risk of MACE. Clinical trial data have established that targeting higher rather that lower Hb levels increases the risk of MACE, yet the Hb target that best balances benefits and risks has never been identified for any of the ESAs.

The US Normal Hematocrit Trial [4] was the first in a series of randomized controlled trials (RCTs) designed to test the hypothesis that a higher target hematocrit in subjects receiving hemodialysis (HD)

would result in improved outcomes. A cohort of 1233 patients with end-stage renal disease (ESRD) on HD with symptomatic heart failure or ischemic heart disease was randomized (open-label) to either partial treatment of anemia (hematocrit of 30 ± 3%) or full correction (hematocrit of 42 ± 3%). The primary endpoint was death or first non-fatal MI, analyzed by time to event. The trial was terminated at the third interim analysis for futility and potential harm in the full anemia correction group. There were 202 primary endpoint events in the full correction group compared to 164 events in the partial correction group: risk ratio 1.3 (95% confidence interval [CI] 0.9–1.9). Also, 39% of subjects in the full anemia correction group had vascular access clotting vs. 29% in the partial treatment arm (P = 0.001).

The CHOIR study [5] was a randomized, open-label, active-controlled clinical trial in patients with NDD-CKD that aimed to show superiority of full anemia correction by ESA administration in terms of cardiovascular events and death. In this trial, 1,432 patients with CKD and anemia (Hb < 11 g/dL) received epoetin alfa and were randomly assigned to a target Hb of either 13.5 g/dL or 11.3 g/dL. The primary endpoint was a composite of death, MI, hospitalization for congestive heart failure, or stroke. The study was also prematurely stopped for futility after an interim analysis at a median study duration of 16 months because it was considered unlikely that benefit would be demonstrated for the primary composite cardiovascular endpoint. In fact, there were 125 events among 715 subjects in the high-Hb group vs. 97 events among 717 subjects in the low-Hb group (hazard ratio [HR], 1.34; 95% CI, 1.03 to 1.74; P = 0.03), with death and hospitalization for heart failure accounting for 75% of the events.

The CREATE study [6] in 603 patients with CKD stages 3–5 (26% with diabetes) failed to demonstrate the superiority of full anemia correction (Hb target 13.0 to 15.0 g/dL) with respect to cardiovascular events, as compared to partial correction of anemia (Hb target 11.0 to 12.5 g/dL), when starting ESA therapy at an earlier stage than ESRD.

Subsequently, TREAT, by far the largest trial, examined cardiovascular and kidney outcomes in 4038 patients with Stage 3 and 4 CKD [7]. TREAT was the only large placebo-controlled study to assess cardiovascular outcomes. Patients received either darbepoetin-alfa to achieve a Hb target of 13.0 g/dL or matching placebo with rescue darbepoetin-alfa when the Hb concentration was < 9.0 g/dL. The HR for the first co-primary endpoint, the composite of death or a cardiovascular event, was 1.05 (p=NS). The HR for the second co-primary endpoint, death or ESRD, was 1.06 (p=NS). There was, however, a nearly two-fold increased risk of stroke (HR 1.92; 95% CI 1.38–2.68) in the higher vs. lower Hb group, in patients both with and without a past history of stroke. In addition, venous thromboembolic events occurred significantly more frequently in the high Hb arm (2.0%) compared to the placebo arm (1.1%, p=0.02).

Based on these clinical trial data and safety surveillance, the ESA labeling was revised again to include the aforementioned warnings.

The international 2012 Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Evaluation and Management of Anemia of Chronic Kidney Disease [8] recommends addressing all correctable causes of anemia (including iron deficiency and inflammatory states) prior to initiation of ESA therapy. The guideline recommends balancing the potential benefits of reducing blood transfusions and anemia-related symptoms against the risks of harm in individual patients (e.g., stroke, vascular access loss, hypertension) (1B). For adult patients with NDD-CKD and Hb concentration < 10.0 g/dL, the decision whether to initiate ESA therapy can be individualized based on the rate of fall of Hb concentration, prior response to iron therapy, the risk of needing a transfusion, the risks related to ESA

therapy, and the presence of symptoms attributable to anemia (2C). For adult patients with NDD-CKD and Hb concentration ≥ 10.0 g/dl, ESA therapy is not recommended (2D). For adult patients with CKD stage 5 on dialysis, ESA therapy is recommended when the Hb is between 9.0 and 10.0 g/dL (2B), and the KDIGO Guideline advises against use to maintain Hb above 11.5 g/dL (2C).

Hypoxia-inducible Factor Prolyl Hydroxylase Inhibitors

Hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF PHIs) represent a new class of orally administered ESAs. The applicant states the following in the Mechanism of Action section of their proposed roxadustat label:

> "Through the inhibition of HIF-PH, roxadustat stimulates a coordinated erythropoietic response that includes the increase of plasma endogenous erythropoietin (EPO) levels, regulation of iron transporter proteins and reduction of hepcidin. This results in improved iron bioavailability, increased hemoglobin production and increased red cell mass."

The applicant hypothesizes that by avoiding the undesirable effects of excess exogenous erythropoietin, roxadustat may have advantages over currently available ESAs, beyond the convenience of an oral dosing form.

Commentary for the Committee

Erythropoiesis stimulating agents are indicated to treat the anemia of CKD based on their ability to increase Hb; however, clinical benefits (i.e., improvements in how patients feel, function, or survive) have not been demonstrated in adequate and well controlled trials. The anemia of CKD has been associated with decreased energy, well-being, and quality of life, as well as cognitive impairment. Although ESAs have been purported to improve these parameters, adequate and well controlled trials have not borne this out. As noted above, sizable randomized trials have attempted to demonstrate that use of ESAs to raise Hb to higher targets improves clinical outcomes, but instead, all have shown (or tended to show) adverse cardiovascular outcomes, leading to limitations on Hb targets as well as a boxed warning, the highest level of warning in product labeling.

ESAs can reduce the need for RBC transfusions, a clear benefit. Although the direct risks of transfusion are now rare (blood-borne infections, transfusion reactions, fluid overload), transfusion avoidance is particularly important in the ESRD population. Importantly, RBC transfusions can cause allosensitization that increases the likelihood of transplant rejection.

The cost of reduced RBC transfusions can be sizable. When ESAs are used to target excessive Hb concentrations, they increase the risk of death, MI, stroke, congestive heart failure, thrombosis of vascular access, and other thrombotic events. They can also cause hypertension and seizures. ESAs also carry warnings for shortened overall survival and increased risk of tumor progression/recurrence in patients with certain malignancies. Given that all of the Hb targeting studies have shown increased cardiovascular risks with higher, rather than lower, Hb targets, it might be assumed that these risks can be reduced by targeting lower Hb values, but it is not known if they can be prevented at any Hb target. No study has identified the optimum Hb target.

In light of these concerns, in 2010, FDA asked the Cardiovascular and Renal Drugs Advisory Committee to opine on whether ESA's indication for the treatment of anemia should be withdrawn in the NDD

patient population. Votes were strongly in favor of continued marketing: 1 "yes," 15 "no," and 1 abstention.

Roxadustat is a first-in-class inhibitor of HIF-PH enzymes. By reducing exposure to intermittent supraphysiologic doses of erythropoietin and improving iron metabolism and availability, the drug was hoped to achieve efficacy at least comparable to ESAs, with fewer safety issues. Moreover, the agent's oral route of administration is unquestionably an important convenience factor for patients who are not on hemodialysis. For patients on hemodialysis, ESAs are recommended to be given by the intravenous route, and the advantage of an oral preparation seems less obvious.

You will discover that roxadustat's efficacy is comparable to that of ESAs; however, there are important risks of serious thromboembolic events, as well as other risks, with roxadustat. Thus, both ESAs and roxadustat have pro-thrombotic effects. This observation raises important questions for discussion. First, how should roxadustat's risks be considered in the context of its benefits? Second, what are the causes of the thrombotic risk that is now observed across classes, and what are the contributing factors? It may help to revisit the questions that arose from the Hb targeting studies [9]. Is the thrombotic risk an on-target effect, mediated through effects on RBC production and related factors, or is it an off-target effect? If the risks are an on-target effect, they may be related to excess Hb concentration, Hb overshoots, excessive rates of Hb rise, rapid fluctuations in Hb, and changes in blood viscosity or volume. Although off-target effects cannot be ruled out, none are known, and, if such effects exist, they must be related to erythropoietin, whether given exogenously (in the case of ESAs) or stimulated indirectly (in the case of roxadustat). Assuming the thrombotic risk is an on-target effect, it seems plausible that less aggressive dosing schemes (e.g., lower starting doses, smaller dose increments during titration, lower Hb targets) could reduce thrombotic risk; however, this has not been established in any randomized controlled study.

We conducted exploratory analyses to elucidate associations between thromboembolic events and roxadustat dose, Hb concentrations, and Hb rates of rise and decline, identical to those undertaken in FDA's 2001 review of the darbepoetin alfa marketing application [10]. In this case, we asked the applicant to corroborate our findings, and they were able to do so. Indeed, higher rates of Hb rise (and decline) were found to be associated with higher rates of thromboembolic events. In light of these findings, the applicant speculates that thromboembolic risks might be reduced through use of a lower roxadustat starting dose. Their prediction seems plausible, but is unproven. Our findings show only *associations*, without proven cause and effect.

FDA's approval standards state that drugs must be both effective and safe to be approved. Our standards do not state that a drug must be more effective than existing treatment(s) to merit approval, or be safer than existing treatments. Yet when weighing the approval of a new drug, we do consider its benefits and risks in context, including the availability of other therapies. The benefits are difficult to calculate here. The data show that roxadustat decreases the need for RBC transfusions relative to placebo, which is expected and reassuring. The data comparing roxadustat to epoetin alfa with respect to RBC transfusions are less conclusive. And if one believes that the risk of thromboembolic events is greater with roxadustat than ESAs, a critical question is whether lowering the roxadustat starting dose will reduce risk importantly.

The applicant makes the case that ESA hyporesponsiveness in patients with CKD is an important problem in need of better therapies. We agree with this viewpoint; however, the applicant did not generate data showing that patients who are hyporesponsive to ESAs are responsive to roxadustat.

Finally, we note that the roxadustat development program was carried out in two distinct patient populations, with important differences. In the dialysis population, subjects were randomized to roxadustat or epoetin alfa, and subject retention was similar with both treatments. Overall exposure differed by ~11%. Thus, for the purpose of safety analyses, the correction needed for disparate time on study was relatively small, and interpretation of the results of safety analyses is clear-cut.

In the NDD patient population, the applicant carried out placebo-controlled studies in patients who were anemic at baseline, with the possibility of "rescue" therapy if needed. These placebo-controlled studies had the advantage of assessing the safety of roxadustat against a "clean" background; however, many subjects dropped out of the studies, and data from these subjects cannot be considered 'missing at random.' Patients with more advanced disease whose Hb was poorly responsive to the study drug were more likely to leave the study, and experience has shown that such patients are at greater risk of cardiovascular events. As patients who received placebo were more likely to remain anemic, they were more likely to drop out of the study than patients who received roxadustat. Thus, there was a considerable disparity in subject retention between the roxadustat and placebo groups, challenging the interpretation of safety analyses. It seems plausible that the patients who dropped out of the placebo groups in higher numbers were at greater risk of adverse events, yet their time of observation—when they were capable of contributing adverse events—was shortened. Conversely, subjects randomized to roxadustat remained in the studies longer, with greater opportunity to experience adverse events.

Given the above, the assessment of adverse events in the NDD subject population is not straightforward. The results of the analyses depend on how the data were analyzed; specifically, whether the time of observation was limited to the time on-treatment (plus 7 days), extended to last contact (on-study analysis), or truncated at a point between these extremes (e.g., on-treatment plus 28 days). These considerations affect all of the safety analyses, including analyses for MACE.

Draft Points to Consider

The applicant is seeking approval of roxadustat, an oral agent for treatment anemia due to CKD, in adult patients not on dialysis and on dialysis.

Non-dialysis-dependent population:

1. Discuss the benefits and risks of roxadustat in the non-dialysis-dependent (NDD) population.
2. If you have concerns regarding these risks, discuss whether you believe they could be addressed through modification of the treatment algorithm, for example, changes in target hemoglobin (Hb), starting dose, titration scheme, monitoring paradigm.
    a. If you favor changes to the treatment algorithm to enhance safety, should they be tested prior to approval?

Dialysis population:

3. Discuss the benefits and risks of roxadustat in the dialysis-dependent (DD) population.

4. If you have concerns regarding these risks, discuss whether you believe they could be addressed through modification of the treatment algorithm, for example, changes in target Hb, starting dose, titration scheme, monitoring paradigm.
   a. If you favor changes to the treatment algorithm to enhance safety, should they be tested prior to approval?

5. Should roxadustat be approved for treatment anemia due to CKD, in adult patients not on dialysis?
   a. If not, provide your rationale, as well as recommendations for additional data and/or analyses that would support a favorable benefit-risk profile and approval of roxadustat.
6. Should roxadustat be approved for treatment anemia due to CKD, in adult patients on dialysis?
   a. If not, provide your rationale, as well as recommendations for additional data and/or analyses that would support a favorable benefit-risk profile and approval of roxadustat.

Evidence of Efficacy

Roxadustat's evidence of effectiveness for the treatment of anemia due to CKD in adult patients is based primarily on six adequate and well-controlled trials.

Non-dialysis dependent (NDD) population: principal studies included three randomized, placebo-controlled, double-blind studies:

- 1517-CL-0608/ALPS (henceforth referred to as "608" in this document)
- FGCL-4592-060/ANDES (referred to as "060" in this document)
- D5740C00001/OLYMPUS (referred to as "001" in this document)

Study 1517-CL-0610/DOLOMITES (referred to as "610" in this document) differed from those above because it employed an active comparator (darbepoetin alfa), was not double-blind, and was conducted solely in Eastern and Western Europe. The study was ongoing at the time the applicant submitted the New Drug Application, and we received the clinical study report early in the review period.

Dialysis-dependent (DD) population: principal studies included 3 randomized, active-controlled (epoetin alfa), open-label studies:

- FGCL-4592-063/HIMALAYAS (referred to as "063" in this document)
- FGCL-4592-064/SIERRAS (referred to as "064" in this document)
- 5740C00002/ROCKIES (referred to as "002" in this document)

Study 1517-CL-0613/PYRENEES (referred to as "613" in this document) provides supplemental information; the study differs from those above because it employed two active comparators (darbepoetin alfa and epoetin alfa), was conducted exclusively in Europe, and permitted use of an ESA that is not licensed in the US.

In light of the safety concerns of the ESAs, the Division has asked sponsors to assess MACE in development programs for drugs for the treatment of anemia of CKD, in both the NDD and DD populations, as noted above. For the NDD indication, studies 608, 001, and 060 were included in a meta-analysis for MACE. For the DD indication, studies 002, 063 and 064 were included in a MACE meta-analyses. Trials 610 and 613 were not considered sufficiently similar to the others to allow inclusion in the meta-analyses.

NDD Indication

Study Designs

The Phase 3 studies for the NDD population are summarized in Table 2. All were multicenter (global), randomized, controlled studies that evaluated the efficacy of roxadustat in correcting Hb. All patients had stage III to V CKD with baseline eGFR < 60 mL/min/1.73 m^2. The primary efficacy endpoint for the US was the mean Hb change from baseline to the mean level during the evaluation period, defined as Week 28 until Week 52. The proportions of subjects with RBC transfusions was a secondary endpoint.

Table 2: Major Trials in the NDD Population

	Placebo-controlled			ESA-controlled
Design Feature	**Study 001**	**Study 060**	**Study 608**	**Study 610**
Blinding	Double-blind	Double-blind	Double-blind	Open-label
Control	Placebo	Placebo	Placebo	Darbepoetin
Planned Treatment Duration (weeks)	52 - 208	52 - 208	52 - 104	104
Number of Patients	2761	922	594	616
Randomization	1:1	2:1	1:1-->2:1	2:1 --> 1:1
Baseline Hb (g/dL)	< 10.0	≤ 10.0	≤ 10.0	≤ 10.5
Hb target - Correction Period (g/dL)	11.0 ± 1.0	≥ 11.0 and ≥ 1.0 from baseline	≥ 11.0 and ≥ 1.0 from baseline	≥ 11.0 and ≥ 1.0 from baseline
Hb target - Maintenance Period (g/dL)	10.0 - 12.0	10.0 - 12.0	10.0 - 12.0	10.0 - 12.0
Roxadustat starting dose (dose given 3 times/week)				
body weight < 70 kg:	70 mg	70 mg	70 mg	70 mg
body weight > 70 kg:	70 mg	100 mg	100 mg	100 mg

Patients with New York Heart Association Class III or IV congestive heart failure (CHF) at enrollment, and patients who had an MI, acute coronary syndrome, stroke, seizure, or a thromboembolic event within 12 weeks prior to randomization were excluded. Patients with uncontrolled hypertension were also excluded. The trials had recommendations for rescue therapy (i.e., iron, ESAs, or transfusion).

The algorithm for dosage adjustments is shown in Table 3. Adjustment was based on the Hb level and the change in Hb over the previous 4 weeks.

Table 3: Roxadustat Dose Adjustment Algorithm for NDD-CKD Subjects

Change in Hb over Past 4 weeks (g/dL)	Correction Period*	Maintenance Period			
		Hb < 10.5 g/dL	Hb 10.5-11.9 g/dL	Hb 12.0-12.9 g/dL	Hb ≥13.0 g/dL
< -1.0	↑	↑	↑	No change	Hold dosing, check Hb and resume dosing when Hb <12.0 g/dL, at a dose that is reduced by two dose steps
-1.0 to 1.0	↑	↑	No change	↓	
> 1.0	No change	No change	↓	↓	

Abbreviations: ↑ = dose increase; ↓ = dose reduction; Hb = hemoglobin

Source: FibroGen Summary of Clinical Efficacy p. 147

Dose increases and reductions:

- Roxadustat dose increases (↑) and reductions (↓) were intended to be preset according to dose steps: 20, 40, 50, 70, 100, 150, 200, 250, and 300 mg. For example, a dose increase at 70 mg would result in a new dose of 100 mg. A dose reduction at 200 mg would result in a new dose of 150 mg.
- The suggested maximum dose was 3.0 mg/kg or 300 mg per administration, whichever was less.

Dose adjustment for rapid Hb increase:

- For Hb increases >2.0 g/dL in 4 weeks, the dose was to be reduced by one dose step immediately.
- Only one dose reduction for rapid Hb increase was recommended within a 4-week period.

Results

Demographic and Baseline Characteristics: Demographic and baseline disease characteristics were generally well balanced between the two treatment groups for the three trials. The mean age of patients was approximately 63 years. Twenty-one percent of patients were age 75 or greater. A majority of the patients were female (58%). Approximately half the patients were Caucasian, 8% were Black, and 36% were Asian. Most were not on prior ESA treatment. Approximately one-quarter of patients were from the US. More than one-third of patients had a history of cardiovascular, cerebrovascular, or thromboembolic disease. More than 90% of trial participants reported hypertension, and diabetes mellitus was reported as a baseline condition by 37% to 65% of trial participants. The baseline Hb was 9.1 g/dL in both treatment groups. The mean eGFR at baseline was approximately 20 mL/min/1.73 m^2 for all studies.

Table 4: Selected Demographics and Baseline Disease Characteristics—NDD Trials

Trial	001		060		608	
Characteristic	**Roxadustat (N=1384)**	**Placebo (N=1377)**	**Roxadustat (N=616)**	**Placebo (N=306)**	**Roxadustat (N=391)**	**Placebo (N=203)**
Age in years mean (SD)	60 9 (14.7)	62.4 (14.1)	64.9 (12.6)	64.8 (13.2)	60.6 (13.5)	61.7 (13.8)
Female, n (%)	820 (59.2)	774 (56.2)	375 (60 9)	176 (57 5)	222 (56.8)	104 (51.2)
Race, n (%)						
White	623 (45.0)	611 (44.4)	176 (28.6)	99 (32.4)	335 (85.7)	182 (89.7)
Black	112 (8.1)	115 (8.4)	76 (12.3)	28 (9.2)	10 (2.6)	3 (1.5)
Asian	544 (39.3)	539 (39.1)	310 (50 3)	151 (49 3)	9 (2.3)	0 (0)
Native Hawaiian or other Pacific Islander	0 (0)	2 (0.1)	2 (0.3)	4 (1.3)	NR	NR
American Indian or Alaska Native	24 (1.7)	29 (2.1)	6 (1.0)	1 (0.3)	NR	NR
Other	81 (5.9)	82 (6.0)	46 (7.5)	23 (7.5)	37 (9.5)	18 (8.9)
Ethnic Group, n (%)						
Hispanic or Latino	344 (24.9)	357 (25.9)	165 (26.8)	84 (27.5)	NR	NR
eGFR (mL/min/1.73m^2) (SD)	19.7 (11.7)	20.0 (11.7)	21.9 (11.5)	22.4 (11.4)	16.5 (10.2)	17 2 (11.7)
Hb Mean (SD)	9.11 (0.73)	9.10 (0.74)	9.10 (0.75)	9.09 (0.69)	9.08 (0.76)	9.10 (0.72)
Prior ESA use, n (%)	15 (1.1)	13 (0.9)	130 (21 3)	48 (15.7)	45 (11.5)	24 (11.8)
Iron Replete, n (%)	809 (58.5)	799 (58.0)	373 (60.6)	170 (55.6)	204 (52.2)	109 (53.7)
Diabetes, n (%)	793 (57.3)	807 (58.6)	395 (64.6)	199 (65 2)	146 (37.3)	89 (43.8)
Cardiovascular disease, n (%)	410 (29.6)	420 (30.5)	210 (34.4)	101 (33.1)	141 (36.1)	89 (43.8)
Cerebrovascular disease, n (%)	105 (7.6)	120 (8.7)	81 (13.3)	39 (12.8)	26 (6.6)	20 (9.9)
Thromboembolic disease, n (%)	30 (2.2)	22 (1.6)	11 (1.8)	3 (1.0)	9 (2.3)	2 (1.0)

Patient Disposition and Discontinuation: For the three studies overall, 62% and 41% of patients randomized to roxadustat and placebo, respectively, completed the treatment period. Decisions to withdraw by either the patient or physician accounted for approximately half of all discontinuations in both groups (Table 5). Discontinuation for ESA rescue therapy was ~4 times higher in patients who received placebo (13.4%) than in roxadustat-treated patients (3.2%). The percentage of patients who discontinued in association with an adverse event(s) was higher among patients treated with roxadustat (6.3%) than in subjects randomized to placebo (4.4%). Deaths were also more frequent in patients randomized to roxadustat (3.4%) than in those randomized to placebo (1.6%).

Table 5: Patient Disposition (NDD Safety Population)

N (%)	Roxadustat (N=2386)	Placebo (N=1884)
Intent-to-treat population	2391	1886
Treated patients	2386 (99.8)	1884 (99.9)
Completed treatment	1485 (62.2)	769 (40.8)
Discontinued treatment early	901 (37.8)	1115 (59.2)
Adverse events	150 (6.3)	83 (4.4)
Death	81 (3.4)	30 (1.6)
Received > 2 courses of ESA rescue therapy	76 (3.2)	252 (13.4)
Lost to follow-up	33 (1.4)	74 (3.9)
Dialysis initiation or kidney transplant	47 (2.0)	20 (1.1)
Physician decision	49 (2.1)	67 (3.6)
Subject decision	250 (11.0)	390 (20.7)
Withdrawal by subject or guardian	144 (6.1)	144 (7.7)
Other	71 (2.9)	55 (2.9)

Drug Exposure: Overall, the duration of study drug exposure was greater in patients treated with roxadustat (mean 84.6 weeks per patient; total 3871 patient-years) than in patients who received placebo (mean 64.3 weeks per patient; total 2323 patient-years). Approximately 71% of roxadustat-treated patients received the drug for > 52 weeks and 34% received it for > 104 weeks. The applicant attributed the higher overall drug exposure in roxadustat-treated patients to the 2:1 randomization ratio (roxadustat:placebo) in the two smaller studies (060 and 608) and the higher dropout rate in patients who received placebo, mainly due to lack of efficacy in all three studies.

Primary Endpoint

As noted above, the primary endpoint in the three principal studies was the mean change in Hb from baseline to the evaluation period (mean value during Weeks 28-52), regardless of rescue therapy, using the intention-to-treat (ITT) analysis set. Efficacy analyses were performed separately for each study. Roxadustat would be considered superior to placebo if the difference in the mean change from baseline between the two treatment groups was statistically significant ($p < 0.05$) using a multiple imputation analysis of covariance (ANCOVA) method. All three studies demonstrated statistically significant results with respect to change in Hb, and FDA was able to corroborate the applicant's findings (Table 7).

Table 6: Drug Exposure in NDD Population

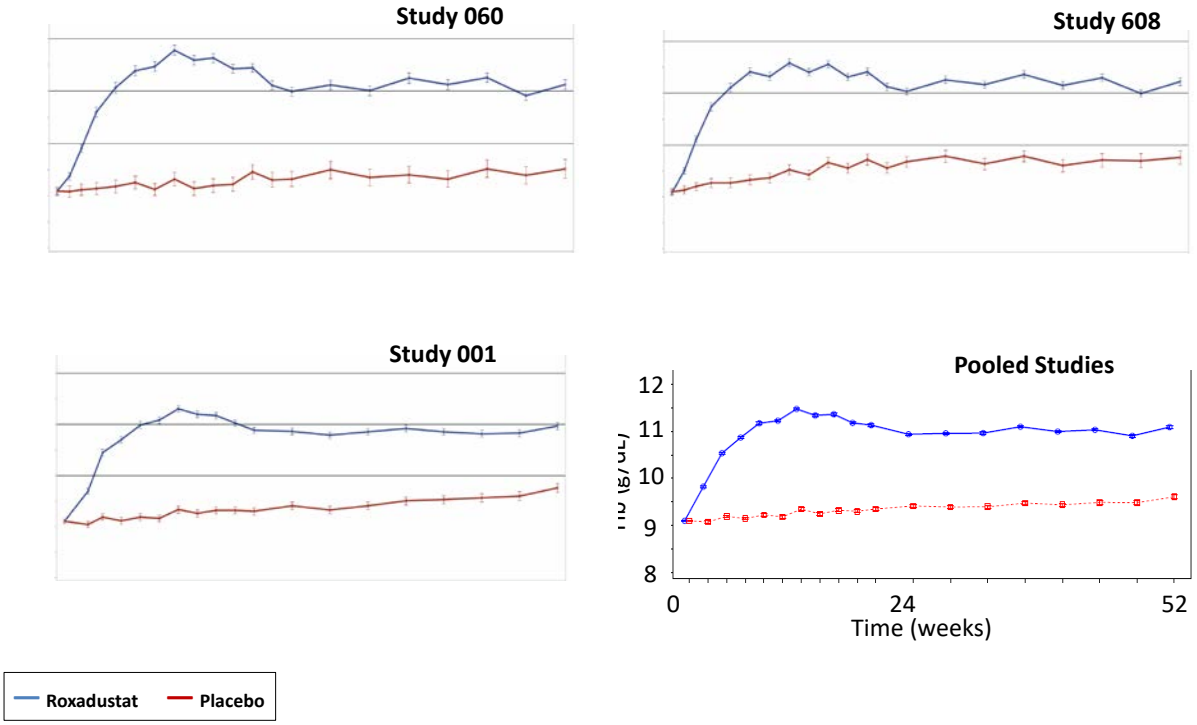
	Roxadustat (N=2386)	Placebo (N=1884)
Duration of exposure (weeks)		
Mean (SD)	84.6 (48.8)	64.3 (44.8)
Median (min, max)	87.1 (0, 235)	57.1 (0, 208)
Exposure (patient-years [PY])	3870.7	2323.2
Study 001	2263.1	1747.6
Study 060	1134.9	377.3
Study 608	472.7	198.3
Weeks of exposure, n (%)		
≤ 4 Weeks	86 (3.6)	81 (4.3)
> 4 Weeks	2300 (96.4)	1803 (95.7)
> 26 Weeks	2020 (84.7)	1389 (73.7)
> 52 Weeks	1694 (71.0)	1005 (53.3)
> 104 Weeks	812 (34.0)	397 (21.1)
Duration of exposure in patients with baseline eGFR <10 (weeks)	**(N=481)**	**(N=358)**
Mean (SD)	72.3 (50.2)	47.8 (41.2)
Median (min, max)	67.7 (0, 216)	32.3 (0, 164)

Table 7: Efficacy Endpoints for NDD Trials

Trial/Treatment Arm	001		060		608	
	Roxadustat N=1384	Placebo N=1377	Roxadustat N=616	Placebo N=306	Roxadustat N=391	Placebo N=203
Mean baseline Hb (SD)	9.11 (0.73)	9.10 (0.74)	9.10 (0.75)	9.09 (0.69)	9.08 (0.76)	9.10 (0.72)
Mean Hb Week 28–52 (SD)	10.84 (0.86)	9.50 (1.18)	11.10 (0.70)	9.25 (1.06)	11.16 (0.84)	9.60 (1.02)
Hb change from baseline to average Hb in Weeks 28 to 52 (SE)	1.75 (0.03)	0.40 (0.03)	2.00 (0.95)	0.16 (0.89)	1.99 (0.95)	0.41 (0.98)
Least squares mean (LSM) difference roxadustat from placebo (95% CI)	1.35 (1.27, 1.43) P < 0.001		1.85 (1.74, 1.97) P < 0.0001		1.69 (1.52, 1.86) P < 0.001	
Subjects with RBC transfusions, N (%)	176 (12.7)	320 (23.3)	34 (5.6)	47 (15.4)	33 (8.5)	39 (19.2)
Hazard Ratio; Nominal P-value	0.37; <0.001		0.26; < 0.001		0.34; <0.001	

Figure 1 shows the results graphically for the three individual studies as well as the pooled studies. On average, the Hb appears to plateau at target at approximately 12 weeks (~8 weeks in study 608).

Figure 1: Changes in Hb over Time—NDD Studies



Source: FDA analysis

Study 610

Study 610 was a multicenter, European, randomized, controlled trial in patients with NDD-CKD. The study differed from the others in that there was an active comparator (darbepoetin alfa), the study was open-label, and the study was conducted exclusively in Europe. The randomization scheme was initially 2:1 (version one of protocol) but changed to 1:1 (version two).

The starting roxadustat dose was 70 mg for body weight < 70 kg and 100 mg for body weight ≥ 70 kg three times a week. Dose titration was conducted based upon the Hb target of 11 ± 1 g/dL. Darbepoetin alfa was dosed subcutaneously or intravenously according to the EU labeling.

The primary efficacy endpoint was the percentage of Hb responders during the first 24 weeks of treatment. A responder was defined as a subject who attained a Hb response as follows:

- Hb ≥ 11.0 g/dL and an increase from baseline ≥ 1.0 g/dL (subjects with baseline Hb > 8.0 g/dL); or
- An increase from baseline ≥ 2.0 g/dL (subjects with baseline Hb ≤ 8.0 g/dL)

Patients receiving rescue therapy were non-responders.

Noninferiority was to be declared if the lower bound of the two-sided 95% CI was > -15%. The primary endpoint was to be analyzed using the Per Protocol Analysis set, consisting of all randomized patients who received ≥ 1 dose of study drug, had ≥ 1 post-dose Hb assessment, and did not meet any exclusion criteria.

Demographic and baseline disease characteristics were comparable between the two treatment groups (Table 8). Mean age was 66 years. The majority of patients were Caucasian (95%), and approximately 56% were women. Approximately 30% were from Western Europe, with 70% from Eastern Europe. In both treatment groups, the mean baseline Hb was 9.55 g/dL and the mean baseline eGFR was 20.3 mL/min/1.73 m^2. Just under half of all patients had a history of cardiovascular, cerebrovascular, or thromboembolic disease.

Table 8: Selected Demographic and Baseline Disease Characteristics—Study 610

	Treatment Groups	
	Roxadustat (N=323)	**Darbepoetin (N=293)**
Age in years mean (SD)	66.8 (13.6)	65.7 (14.4)
Female, n (%)	178 (55.1%)	164 (56.0%)
Race, n (%)		
Caucasian	306 (94.7%)	281 (95.9%)
Black	8 (2.5%)	2 (0.7%)
Asian	9 (2.8%)	10 (3.4%)
Baseline eGFR (mL/min/1.73m^2) (SD)	20.3 (11.5)	20.3 (10.7)
Baseline Hb mean (SD)	9.55 (0.75)	9.55 (0.69)
Baseline iron replete, n (%)	182 (56.3%)	152 (51.9%)
Diabetes, n (%)	150 (46.5%)	137 (46.7%)
History of cardiovascular, cerebrovascular, or thromboembolic disease, n (%)	152 (47.1%)	142 (48.5%)

Patient Disposition and Discontinuations

Study retention was similar in the two treatment groups: 22.9% of patients in the roxadustat group vs. 19.8% in the darbepoetin alfa group withdrew before the Week 24 cutoff. The most frequent reasons for discontinuation in the roxadustat group were withdrawal by patient (9.9%), death (8.4%), and adverse events (6.5%). The most common reasons for discontinuation in the darbepoetin group were death (10.2%), withdrawal by patient (6.8%), and adverse event (2.7%).

Efficacy Endpoint

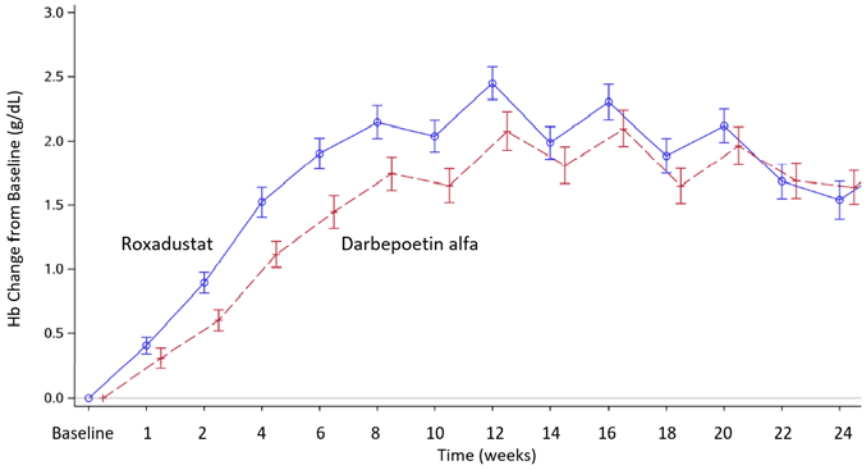
For the per-protocol analysis set, 89.5% of patients in the roxadustat group vs. 78.0% in the darbepoetin alfa group were responders (Table 9). The difference in proportions was 11.5%, favoring roxadustat, and the 95% CI of the response rate difference excluded -15%, meeting the study's efficacy objective.

The changes in Hb are shown graphically in Figure 1. Although the rate of Hb rise was not evaluated as a study endpoint, a trend showing more rapid Hb increase in the roxadustat group is clearly evident, which may have ramifications for safety.

Table 9: Efficacy Results for Trial 610 (Ns Represent Numbers in the Per-protocol Analysis Set)

	Roxadustat N=286	Darbepoetin alfa N=272
Number of responders	256 (89.5%)	213 (78.0%)
95% CI	(85.4%, 92.8%)	(72.6%, 82.8%)
Difference of proportions (roxadustat – darbepoetin alfa)	11.5%	
95% CI of difference	(5.66%, 17.36%)	

Figure 2: Hb Change from Baseline by Time (mean ± 95% CI)—Study 610 (figure adapted from applicant)



DD Population

Study Designs

Roxadustat's efficacy for the treatment of anemia in adult patients with DD-CKD is supported by three randomized, active controlled, non-inferiority trials: 002, 063, and 064. These were similarly designed, open-label studies where subjects were randomized 1:1 to roxadustat or epoetin alfa. All subjects had Stage 3 to 5 CKD with a baseline Hb level < 10 g/dL (if not on an ESA) or < 12 g/dL (if on an ESA). All trials excluded patients with New York Heart Association Class III or IV CHF at enrollment, and patients with a history of MI, acute coronary syndrome, stroke, seizure, or thrombotic event within 12 weeks prior to enrollment. Patients with uncontrolled hypertension were also excluded. The intended duration was ≥ 52 weeks. The trials had recommendations for rescue therapy using ESAs or transfusion in the roxadustat group and transfusion in the epoetin alfa group. The roxadustat dose was titrated to achieve a Hb target of 10.0 to 11.0 g/dL in the US and 10.0 to 12.0 g/dL outside the US. The primary endpoint for the three studies was the mean change in Hb from baseline to Weeks 28 to 52, regardless of rescue therapy. Having determined the mean treatment effect in both groups, non-inferiority (NI) of roxadustat to epoetin alfa was to be declared if the lower bound of the 95% CI of the inter-group difference

(roxadustat - epoetin alfa) was greater than the pre-defined NI margin -0.75 g/dL, i.e., the 95% CI excluded a difference of 0.75 g/dL or more. The proportions of subjects with RBC transfusions was a secondary endpoint. Major design features are summarized in Table 10.

Study 002 enrolled patients with ESRD who were receiving, or had initiated, hemodialysis or peritoneal dialysis at least 30 days prior to enrollment. Amendment #6, designed to increase enrollment of US patients with incident dialysis, changed the dialysis criterion to receiving at least 2 weeks and not more than 4 months. At enrollment, subjects could be on an ESA (with Hb <12.0 g/dL) or not on an ESA (with Hb <10 g/dL). For patients not on an ESA, the roxadustat starting dose was 70 mg orally thrice weekly regardless of body weight; for patients on an ESA, the starting dose was calculated on the basis of the ESA dose (range: 70 to 200 mg thrice weekly).

Study 063 enrolled patients with CKD and incident dialysis (2 weeks to 4 months prior to randomization), with baseline Hb $\leq$ 10 g/dL. The roxadustat starting dose was 70 mg for body weight < 70 kg and 100 mg for body weight $\geq$ 70 kg, thrice weekly.

Study 064 enrolled subjects who were on a stable ESA dose $\geq$ 4 weeks prior to and during screening, with an allowable Hb range of 8.5 to 12.0 g/dL. Amendment #1 and #2 encouraged the enrollment of more patients considered to have incident dialysis as defined for Study 063. The starting roxadustat dose was 70 to 200 mg thrice weekly, calculated on the basis of the prior ESA dose.

Only Study 063 enrolled exclusively incident dialysis. The other studies amended their protocols to enroll incident dialysis and planned to later compare results between incident and stable dialysis subgroups. Incident dialysis did not have a standard definition. Because of the multiple amendments and lack of a standardized definition, FDA did not further analyze this subgroup.

Study 613, described separately, was conducted in Eastern, Central, and Western Europe, and used both darbepoetin alfa and epoetin alfa as comparators. Use of an ESA, approved in the EU but not licensed in the US, was permitted.

Table 10: Major Trials in the DD Patient Population

	Major Studies			Supportive Study
Design Feature	**Study 002**	**Study 063**	**Study 064**	**Study 613**
Blinding	Open-label	Open-label	Open-label	Open-label
Control	Epoetin alfa	Epoetin alfa	Epoetin alfa	Epoetin alfa/ darbepoetin alfa
Planned treatment duration (years)	< 4	< 4	< 4	1 - 2
Number of Patients	2106	1043	741	836
Randomization	1:1	1:1	1:1	1:1
Baseline Hb (g/dL)	< 10.0 ‡; <12.0	≤ 10.0	9.0 † to 12.0	9.5 to 12.0
Stable dialysis (SD); incident dialysis (ID); dialysis-dependent (DD)	SDD and ID-DD	ID-DD	SDD and ID-DD	SDD
Hb target - Maintenance Period (g/dL)	10.0 - 12.0 §	10.0 - 12.0 §	10.0 - 12.0 §	10.0 - 12.0
Hb correction or conversion	Correction and conversion	Correction	Conversion	Conversion

† ≥ 8.5 g/dL for ID-DD patients; ‡ For subjects not on an ESA
§ 10.0 to 11.0 g/dL in the US; 10.0 to 12.0 g/dL outside the US
ID-DD = incident dialysis; SDD = stable dialysis-dependent

Dosage adjustment was based on the Hb level and the change in Hb over the previous 4 weeks, and was the same for all three studies (Table 11).

Table 11: Roxadustat Dosage Adjustment for Studies 063, 064, and 002

Changes in Hb over past 4 weeks	Hb <10.5 g/dL	Hb 10.5 to 11.9 g/dL	Hb 12.0 to 12.9 g/dL	Hb ≥13.0 g/dL
<-1.0	↑	↑	No change	Dose withheld and resumed when Hb was ≤11.9 g/dL, at a dose that was to be reduced by 2 dose steps
-1.0 to 1.0	↑	No change	↓	
>1.0	No change	↓	↓	

Source: Modified FibroGen Table 6 from Clinical Study Report for Study 002

Results

Demographics & Baseline Disease Characteristics

The demographics and baseline disease characteristics for all three trials were generally balanced between the two groups. Overall, approximately 45% of patients were enrolled in US sites. Mean age

was 54 to 58 for all studies. At baseline, most patients were male (58%), White (varied by study), on prior ESA treatment, and on stable dialysis. Study 064 was conducted solely in the US, and 42% of participants were Black. More than 90% of trial participants reported hypertension as a baseline medical condition. Diabetes mellitus was reported as a baseline condition by 28% to 65% of trial participants. Overall, about half of the subjects had a history of cardiovascular, cerebrovascular, or thromboembolic disease. The mean baseline Hb was similar between the two groups, averaging 9.6 g/dL over the three studies. Overall, approximately, 90% of patients in both treatment groups were receiving hemodialysis, and the rest were receiving peritoneal dialysis.

Table 12: Selected Demographics and Baseline Disease Characteristics for DD Trials

Trial	002		063		064	
Characteristic	**Roxadustat (N=1051)**	**Epoetin alfa (N=1055)**	**Roxadustat (N=522)**	**Epoetin alfa (N=521)**	**Roxadustat (N=370)**	**Epoetin alfa (N=371)**
Age mean (SD) (years)	53.5 (15.3)	54 5 (15.0)	53.8 (14.7)	54.3 (14.6)	57.6 (13.6)	58.4 (13.3)
Female, n (%)	426 (40.5)	429 (40.7)	213 (40.8)	214 (41.1)	183 (49.5)	156 (42.0)
Race, n (%)						
White	597 (56.8)	598 (56.7)	415 (79.5)	400 (76.8)	165 (44.6)	184 (49.6)
Black	148 (14.1)	158 (15.0)	44 (8.4)	50 (9.6)	158 (42.7)	156 (42.0)
Asian	208 (19.8)	198 (18.8)	43 (8 2)	51 (9.8)	21 (5.7)	15 (4.0)
Native Hawaiian or other Pacific Islander	5 (0.5)	3 (0.3)	NR	NR	1 (0.3)	3 (0.8)
American Indian or Alaska Native	50 (4.8)	62 (5.9)	1 (0.2)	4 (0.8)	10 (2.7)	7 (1.9)
Other	43 (4.1)	36 (3.4)	19 (3.6)	16 (3.1)	15 (4.1)	6 (1.6)
Hispanic or Latino	268 (25.5)	271 (25.7)	99 (19.0)	77 (14.8)	137 (37.0)	129 (34.8)
US subjects, n (%)	385 (36.6)	391 (37.1)	127 (24.3)	125 (24.0)	370 (100)	371 (100)
Hemodialysis, n (%)	938 (89.2)	938 (88.9)	469 (89.8)	462 (88.7)	354 (95.7)	354 (95.4)
Peritoneal Dialysis, n (%)	111 (10.6)	117 (11.1)	53 (10.2)	58 (11.1)	16 (4.3)	17 (4.6)
Dialysis Duration > 4 months, n (%)	852 (81.1)	841 (79.8)	2 (0.4)	2 (0.4)	334 (90.3)	336 (90.6)
Baseline Hb Mean (SD) (g/dL)	9.99 (1.20)	10.02 (1.24)	8.43 (1.04)	8.46 (0.96)	10.30 (0.66)	10.31 (0.66)
Diabetes, n (%)	459 (43.7)	454 (43.0)	205 (39.3)	204 (39.2)	250 (67.5)	255 (68.8)
History of cardiovascular, cerebrovascular, or thromboembolic disease, n (%)	305 (29.0)	304 (28.8)	219 (42.0)	224 (43.0)	229 (61.9)	210 (56.6)

Patient Disposition

Of 3890 patients randomized, 3880 were treated (roxadustat = 1940; epoetin alfa = 1940). Treatment completion rates were 58.5% and 66.3% in the roxadustat and epoetin alfa groups, respectively, and reasons for discontinuation are shown in Table 13. Discontinuations were disproportionately higher in the roxadustat group for adverse events, death, and the need for ESA rescue therapy.

Table 13: Patient Disposition DD Safety Population (002, 063, 064)

N (%)	Roxadustat (N=1940)	Epoetin Alfa (N=1940)
Intent-to-treat population	1943	1947
Treated patients	1940 (99.8)	1940 (99.6)
Completed treatment	1135 (58.5)	1287 (66.3)
Discontinued treatment Early	805 (41.5)	653 (33.7)
Adverse events	110 (5.7)	54 (2.8)
Death	141 (7.3)	129 (6.6)
Received > courses of ESA rescue therapy	32 (1.6)	0 (0)
Kidney transplant	115 (5.9)	147 (7.6)
Subject decision	135 (7.0)	88 (4.5)
Withdrawal by subject or guardian	78 (4.0)	78 (4.0)
Physician decision	68 (3.5)	32 (1.6)
Lost to Follow-up	10 (0.5)	5 (0.3)
Others	116 (6.0)	120 (6.1)

Drug Exposure

Figure 3 shows the differential retention of subjects in the roxadustat and ESA groups for the three studies. As predicted by the figure, the mean duration of study drug exposure was shorter in patients randomized to roxadustat (89.2 weeks) than to epoetin alfa (100.7 weeks). Total durations of exposure were 3315 and 3744 patient-years, respectively. The percentages of patients who received the study drug through Week 52 (the end of the assessment period for the primary endpoint) were 63% for roxadustat and 71% for epoetin alfa.

Figure 3: Subject Retention for the DD Population—Studies 002, 063, 064

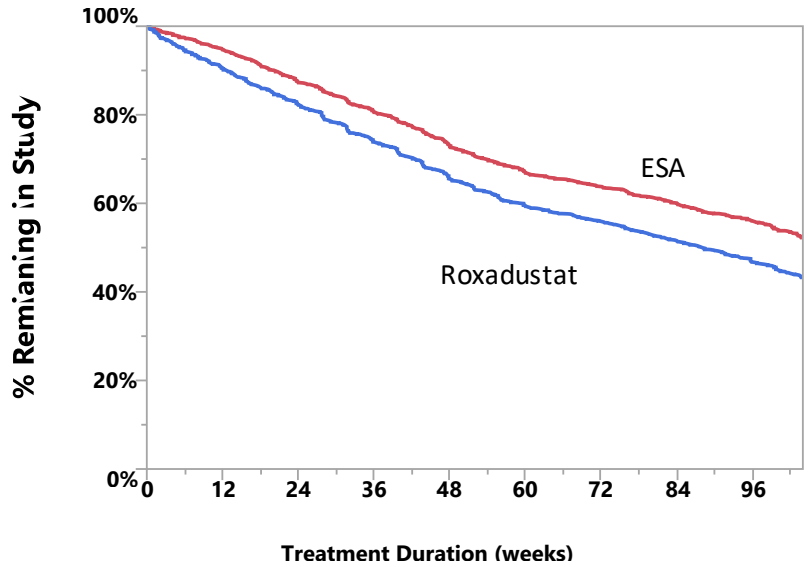


Table 14: Duration of Exposure in DD Population (002, 063, 064)

	Roxadustat (N = 1940)	Epoetin Alfa (N = 1940)
Duration of exposure (weeks)		
Mean (SD)	89.2 (58.6)	100.7 (57.5)
Median (min, max)	87.9 (0, 228)	107.5 (0, 227)
Duration of exposure, mean (years)	1.71	1.93
Exposure by study (patient-years)		
Total	3315.3	3743.6
Study 002	1800.1	2032.7
Study 063	890.7	759.3
Study 064	624.5	951.6
Exposure, n (%)		
≤ 4 Weeks	71 (3.7)	34 (1.8)
> 4 Weeks	1869 (96.3)	1906 (98.2)
> 26 Weeks	1572 (81.0)	1683 (86.8)
> 52 Weeks	1223 (63.0)	1370 (70.6)
> 104 Weeks	831 (42.8)	1010 (52.1)
> 156 Weeks	302 (15.6)	385 (19.8)

Primary Endpoint

All three studies demonstrated non-inferiority of roxadustat vs. epoetin alfa (Table 15), as the lower bound of the 95% CI of the treatment difference (roxadustat - epoetin alfa) exceeded the prospectively-defined NI margin of -0.75 g/dL. Statistically significantly fewer subjects received RBC transfusions in the roxadustat group than in the epoetin alfa group in Study 064; however, Studies 002 and 063 showed opposite trends (Table 15). Moreover, it is important to recognize that the transfusion data are confounded. Subjects who were randomized to roxadustat could receive ESAs or RBC transfusions as a rescue therapy, whereas subjects who were randomized to epoetin alfa could receive only a transfusion as rescue therapy. Thus, it cannot be concluded that subjects who received roxadustat required fewer RBC transfusions than subjects who received epoetin alfa.

Table 15: Efficacy Results for the DD Trials

Study/Treatment Arms	002		063		064	
	Roxadustat N=1051	Epoetin alfa N=1055	Roxadustat N=522	Epoetin alfa N=521	Roxadustat N=370	Epoetin alfa N=371
Mean Baseline Hb (SD)	9.99 (1.2)	10.02 (1.24)	8.43 (1.04)	8.46 (0.96)	10.30 (0.66)	10.31 (0.66)
Hb averaged over Weeks 28–52 (SD)	10.83 (0.94)	10.74 (1.02)	11.00 (0.82)	10.83 (0.88)	10.69 (0.76)	10.22 (0.68)
Change from baseline in Hb average over Weeks 28 to 52 (adjusted mean) (SE)	0.77 (0.04)	0.68 (0.04)	2.38 (0.04)	2.20 (0.04)	0.28 (0.07)	-0.19 (0.06)
Difference: Roxadustat minus Epoetin alfa (95% CI)	0.09 (0.01, 0.18)		0.18 (0.08, 0.29)		0.48 (0.37, 0.59)	
Subjects with RBC transfusions, N (%)	103 (9.8)	139 (13.2)	38 (7.3)	33 (6.4)	46 (12.5)	78 (21.1)
Hazard Ratio; Nominal P-value	0.83; 0.15		1.26; 0.33		0.67; 0.04	

Study 613

Study 613 (Pyrenees) was a randomized, open-label, non-inferiority trial in patients with DD-CKD on stable hemodialysis or peritoneal dialysis for ≥ 4 months and on stable ESA treatment for ≥ 8 weeks. The study was conducted at multiple sites in Eastern, Central, and Western Europe. Patients were randomized 1:1 to roxadustat or continued treatment with their prior ESA: darbepoetin alfa or epoetin alfa. (Of note, randomization was not stratified by prior ESA.) Use of an ESA, approved in the EU but not licensed in the US, was permitted. Eligible patients were required to have a baseline Hb between 9.5 and 12.0 g/dL. The US primary efficacy endpoint was the change in Hb from baseline to the mean level during the evaluation period (weeks 29 through 52), regardless of rescue therapy. Hypothesis testing was conducted with a NI margin of -0.75 g/dL as it was for Studies 002, 063, and 064: i.e., NI would be declared if the 95% CI of the difference excluded 0.75 g/dL or more.

The starting dose of roxadustat was based on the previous ESA dose and the protocol provided for adjusting the roxadustat dose to maintain Hb between 10 and 12 g/dL.

Study Patients: Enrolled patients were randomized to roxadustat (n=415) or continued ESA treatment (n=422) for an intended treatment duration of ≥ 52 weeks (≤ 104 weeks). Approximately 62% of patients had been using epoetin alfa, and approximately 38% had been using darbepoetin alfa.

Demographics and Baseline Characteristics: The demographics and baseline characteristics were generally well balanced between the two groups. The mean age of patients was approximately 61 years. Most patients were male (58%), White (97%), and on hemodialysis (94%). Mean baseline Hb values were approximately 10.8 g/dL in both groups, and the majority of patients were iron replete at baseline.

Study completion rates were 60% in the roxadustat group and 73% in the ESA group. Deaths occurred in 14.9% of subjects in the roxadustat group vs. 11.2% of subjects in the ESA group.

Table 16: Selected Demographic and Baseline Disease Characteristics—Study 613

	Roxadustat (N=415)	Continued ESA Treatment (N=422)
Age, mean (SD)	61 (13.8)	61.8 (13.4)
Female, n (%)	169 (40.8)	285 (44)
Race, n (%)		
White	405 (97.8)	407 (96.9)
Black	6 (1.4)	6 (1.4)
Asian	1 (0.2)	3 (0.7)
Other	2 (0.5)	4 (1.0)
Hemodialysis, n (%)	379 (91.5)	405 (96.4)
Peritoneal Dialysis, n (%)	35 (8.5)	15 (3.6)
Baseline Hb (g/dL), mean (SD)	10.75 (0.62)	10.77 (0.63)
Diabetes, n (%)	104 (25.1)	133 (31.6)
History of cardiovascular, cerebrovascular, or thromboembolic disease, n (%)	169 (40.8)	201 (47.9)

Efficacy Endpoint

For the primary endpoint of Hb change from baseline averaged over Weeks 28 to 52 regardless of rescue therapy, the study met the noninferiority margin of -0.75 g/dL. The least squares mean difference between roxadustat vs. ESA in the ITT was 0.17 (95% CI: 0.082, 0.26) with $p < 0.001$ (one-sided).

Safety

Safety is divided into four sections: (1) analyses of adverse events; (2) analyses of laboratory data; (3) analyses of MACE; and (4) explorations of the relationships between thromboembolic events, drug dose, Hb concentration, and rate of change of Hb concentration. In each section, data for the NDD and DD patient populations are presented sequentially. All of these analyses contribute importantly to the assessment of roxadustat's safety.

Studies in the NDD patient population are placebo-controlled. Consequently, they offer the opportunity to assess the safety of roxadustat against a "clean" background. On the other hand, these studies suffer from disparate rates of discontinuation in two treatment groups. As noted above, patients who were doing poorly, some of whom required RBC transfusions, were more likely to discontinue from treatment and discontinue from the study, such they could no longer contribute adverse events. It follows that adverse event rates are dependent on time of observation. Even when adjusted for observation time, the results may be somewhat skewed against roxadustat. Thus, smaller differences in adverse event rates between the roxadustat and placebo groups in the NDD population may be factitious and should be interpreted carefully. (Larger differences, in contrast, merit concern.) In the DD population, studies

were active-controlled (against epoetin alfa) and rates of discontinuation were similar; therefore, interpretation of adverse event rates in this population is straightforward.

Analyses of Adverse Events

Methods

Pooling: Given that the three studies in the NDD population were similar in terms of their patient populations, durations, and Hb targets, simple pooling was used to combine them for the main safety analyses. Of note, however, the randomization ratios differed across the studies (1:1 in study 001, 2:1 in studies 060 and 608), and the studies differed in size, leading to the potential for Simpson's paradox. Nevertheless, we found that the signals that emerged from the pooled analyses were generally consistent across the individual studies.

Definition of "Treatment-emergent": A "treatment emergent" adverse event is defined as an adverse event that was not present prior to treatment but occurs during treatment (or, if present at treatment initiation, an event that worsens in intensity or frequency on-drug). Only treatment-emergent adverse events are considered in this document, as is customary.

Ascertainment Window: When patients are monitored after treatment discontinuation, it is essential to define the "ascertainment window"—the time on-treatment plus the interval of additional monitoring beyond which a causal relationship between the drug and effect would not be reasonably likely. Typical ascertainment windows are the treatment period plus 5 half-lives; however, in many cases, a week or a month are selected—somewhat arbitrarily.

Establishment of the ascertainment window requires careful consideration. For example, alpha$_1$ adrenoreceptor blocking agents would not be expected to cause orthostatic hypotension once they are no longer in the circulation. In contrast, some drugs have the potential to cause long-term sequelae, e.g., pulmonary fibrosis. Thus, it is important to define the ascertainment window, and this is usually done prospectively.

The applicant conducted analyses based on multiple ascertainment windows: on-treatment plus 7 days (OT+7), on-treatment plus 28 days (OT+28), and on-treatment plus all (OT+All), i.e., On-Study. Although longer "windows" have the potential to detect adverse events with longer latency, they also have greater potential for confounding. (For example, some patients initiated other treatments for anemia after discontinuing the study drug that could confound analyses using longer ascertainment windows.) Thus, results for all three "windows" were considered in some of our analyses and are considered complementary. More detail is provided in the section on MACE.

Adverse Event Queries: Study investigators report adverse events using their own language, i.e., 'verbatim terms,' which must be translated into appropriate, standard preferred terms prior to analysis. For example, the verbatim term 'hypotension w/ sepsis from pneumococcus' would be translated to the standard preferred term 'pneumococcal sepsis.'

Verbatim terms can include substantial detail, and disparate but related terms must be combined in order to represent the various safety signals completely and accurately. Thus, the terms 'wound sepsis,' 'neutropenic sepsis,' 'urosepsis,' 'septic shock,' etc. all indicate 'sepsis' and need to be combined. The combination of medically similar and/or related preferred terms for analysis is called a "query." To be

clear, tabulation of individual preferred terms without queries can be highly deceptive. For example, the adverse event term 'sepsis' was reported for 81 patients who received roxadustat in the NDD population, whereas a query for 'sepsis,' including multiple additional adverse events, finds 132 patients. The preferred terms used in some of the more important queries are shown in the appendix.

Standardized MedDRA queries have been available for many years; however, they are not well suited for assessing adverse events in new drug applications. For this reason, FDA is developing a standard set of queries for new drugs. FDA's new queries, as well as other queries developed over many years by FDA staff, were used to assess the adverse events in the roxadustat development program.

Event rate: In the analysis of adverse events, event rates are reported per 100 patient years (P-Y). These calculations include only the incident event (i.e., recurrent events are not counted) and utilize an overall total exposure (dependent upon the ascertainment window applied) across the set of adverse events. In other words, for subjects who experienced an adverse event, follow-up time was not censored after the event in these analyses. For patients who experienced a particular adverse event, the applicant truncated the time of exposure at the time of event (in some analyses). This is a reasonable approach that differs slightly the approach we used; however, the differences in calculated patient exposure are minimal, with essentially no effect on the results.

Drug-relatedness: The most important consideration when assessing adverse events in the consideration of drug safety is relatedness. Merely identifying a risk difference in an adverse event that disfavors a drug does not constitute causality. In our formulation of causality, we considers a drug's mechanism of action, non-clinical (animal) findings, known effects of other drugs in-class, relationship of the adverse event to dose/exposure, consistency of signals in studies across a development program, and consistency across related adverse events (e.g., signals for orthostatic hypotension and falls are self-reinforcing). Finally, consistency between the total numbers of adverse events and serious adverse events can be important, and may play an important role in considering the overall benefit-risk profile.

Results

NDD Patient Population

The NDD patient population included all 4270 randomized subjects who received ≥ 1 dose of study drug in the three major randomized, double-blind, placebo-controlled studies (001, 060, 068). No subjects were on dialysis at the time of randomization, although some initiated dialysis during the study. Some of the adverse events are relatively specific to hemodialysis (e.g., vascular access thrombosis) or peritoneal dialysis (e.g., peritonitis); however, the actual denominators (i.e., numbers of subjects) are unknown. Thus, although the relative risks of such events may be accurate, their absolute risk differences will be underestimated. Analyses are shown separately for Study 610, which employed an active control group instead of a placebo group.

Deaths

Causes of death were adjudicated by an independent event committee and are summarized in Table 17, as reported by the applicant. Their analysis is based on the OT+28 ascertainment window. The "Patients with Events" columns list the numbers of subjects along with the corresponding percentages of patients. As noted above, however, the mean and total time-on-study differed between the roxadustat and placebo groups; therefore, expression of a simple frequency of adverse events (% of patients) is

potentially misleading. The "Events per 100 P-Y" columns (P-Y = patient-year) is corrected for duration of treatment, and provides a more appropriate basis for comparison between the treatment groups. The "Risk Difference" column (red bars) shows the absolute risk difference between the roxadustat and placebo groups, and represents a simple subtraction expressed per 100 P-Y. The "Relative Risk" column (blue bars) is the ratio of the risks (roxadustat/placebo) based on events per 100 P-Y.

Table 17: Adjudicated Causes of Death—Studies 001, 060, 068; Ascertainment Window OT+28

	Patients with events (%)		Events (per 100 PY)		Risk Difference (per 100 P-Y)	Relative Risk Based on P-Y
	Roxadustat	Placebo	Roxadustat	Placebo		
	N = 2386	N = 1884	4038 P-Y	2460 P-Y		
Total Deaths	260 (10.9)	122 (6.48)	6.44	4.96	1.48	1.30
Cardiovascular-related	105 (4.4)	60 (3.18)	2.60	2.44	0.16	1.07
Sudden cardiac death	48 (2.01)	26 (1.38)	1.19	1.06	0.13	1.12
Acute MI	18 (0.75)	14 (0.74)	0.45	0.57	-0.12	0.78
Stroke	13 (0.54)	8 (0.42)	0.3	0.3	-0.01	0.99
Heart failure	10 (0.42)	10 (0.53)	0.25	0.41	-0.16	0.61
Other cardiovascular	9 (0.38)	2 (0.11)	0.22	0.08	0.14	2.74
Cardiovascular procedure	6 (0.25)	0 (0)	0.15	0.00	0.15	-
Non-cardiovascular-related	128 (5.36)	49 (2.6)	3.17	1.99	1.18	1.59
Infection	55 (2.31)	16 (0.85)	1.36	0.65	0.71	2.09
Renal	44 (1.84)	16 (0.85)	1.1	0.7	0.44	1.68
Malignancy	6 (0.25)	2 (0.11)	0.15	0.08	0.07	1.83
Hemorrhage	5 (0.21)	3 (0.16)	0.12	0.12	0.00	1.02
Undetermined	27 (1.13)	13 (0.69)	0.67	0.53	0.14	1.27

Data are compliled from Table 50 in the applicant's Integrated Summary of Safety; P-Y = patient-year

The rate of death was higher in patients who had received roxadustat; the overall risk difference was 1.48 deaths per 100 P-Y, with a relative risk of 1.30. Somewhat fewer than half the deaths were cardiovascular in nature. The leading causes of death (and the largest contributors to the risk difference) were infections, "renal" deaths, and sudden cardiac deaths. Deaths will be discussed in greater detail in the MACE section. The numbers of adjudicated deaths from malignancy are small, but there are more deaths from malignancy in patients who received roxadustat (estimated relative risk = 1.8). Malignancy is of interest because it is a labeled adverse drug reaction for the ESAs.

Deaths in Study 610

In this study of 616 subjects, there were 22 (6.8%) and 18 (6.1%) deaths in the roxadustat and darbepoetin alfa groups, respectively, in the OT+28 analysis. For the On-study analysis, there were 29 (9.0%) and 22 (7.5%) deaths in the respective groups. The numbers of deaths were greater in the roxadustat group, but the difference is too small to be conclusive.

Serious Adverse Events

Table 18 shows the serious adverse events and adverse event queries for the pooled studies in the NDD patient population for the OT+7 ascertainment window. The tabulation (and many that follow in this document) shows a mixture of serious adverse event *queries* and individual serious adverse event *preferred terms*, with the later denoted by "term or "actual term." Subjects with more than one serious adverse event for a given preferred term or more than one event within the same query were counted only once.

Adverse events and adverse event queries for which the event rate (per 100 P-Y) is ≥ 0.5 with a relative risk ≥ 1.3 are shown, along with adverse events of special interest.

Table 18: Serious Adverse Events—Studies 001, 060, and 608; Ascertainment Window OT+7

	Patients with events (%)		Events (per 100 PY)		Risk Difference (per 100 P-Y)	Relative Risk Based on P-Y
	Roxadustat	Placebo	Roxadustat	Placebo		
	N = 2386	N = 1884	3871 P-Y	2323 P-Y		
Thromboembolic						
Thrombotic events	140 (5.87)	58 (3.08)	3.62	2.50	1.1	1.45
Device/shunt thrombosis	36 (1.51)	8 (0.42)	0.93	0.34	0.6	2.70
Deep vein thrombosis (term)	20 (0.84)	2 (0.11)	0.52	0.09	0.4	6.00
Myocardial infarction FDA	54 (2.26)	31 (1.65)	1.40	1.33	0.1	1.05
Stroke	53 (2.22)	26 (1.38)	1.37	1.12	0.3	1.22
Ischemic stroke	31 (1.30)	14 (0.74)	0.80	0.60	0.2	1.33
Pulmonary embolism (term)	8 (0.34)	1 (0.05)	0.21	0.04	0.2	4.80
Central Nervous System						
Intracranial hemorrhage	24 (1.01)	6 (0.32)	0.62	0.26	0.4	2.40
Seizure FDA	9 (0.38)	1 (0.05)	0.2	0.0	0.2	5.40
Infection						
Sepsis/septic shock	87 (3.65)	22 (1.17)	2.25	0.95	1.3	2.37
Urinary tract infection	100 (4.19)	53 (2.81)	2.58	2.28	0.3	1.13
Infection, bacterial	49 (2.05)	17 (0.9)	1.27	0.73	0.5	1.73
Cellulitis	36 (1.51)	13 (0.69)	0.93	0.56	0.4	1.66
Bacteremia	30 (1.26)	10 (0.53)	0.8	0.4	0.4	1.80
Peritonitis	28 (1.17)	10 (0.53)	0.72	0.43	0.3	1.68
Miscellaneous						
Acute kidney injury (term)	75 (3.14)	34 (1.8)	1.94	1.46	0.5	1.32
Hyperkalemia (term)	56 (2.35)	22 (1.17)	1.45	0.95	0.5	1.53
Fracture	45 (1.89)	19 (1.01)	1.16	0.82	0.3	1.42
Gastrointestinal hemorrhage	58 (2.43)	29 (1.54)	1.50	1.25	0.3	1.20
Hyponatremia (term)	22 (0.92)	9 (0.48)	0.57	0.39	0.2	1.47
Malignancy FDA	37 (1.55)	23 (1.22)	0.96	0.99	0.0	0.97

Listings labeled "term" represent individual preferred terms.

All other listings represent queries that combine multiple, related adverse event terms.

FDA = FDA query; P-Y = patient-year

Given the problem of differential dropout from the two treatment groups, relative risks less than ~1.3 seem difficult to interpret. The ESAs are known to increase the risk of thrombotic events, and they are listed as adverse drug reactions in their labeling. Roxadustat also shows an obvious signal for serious thrombotic events, with an estimated risk difference (vs. placebo) of 1.1 events per 100 P-Y and a relative risk of 1.45.[1] The largest contributors to the thrombosis query are MI, with 54 events in the roxadustat group, and stroke with 53 events. The numbers of subjects with deep vein thrombosis and pulmonary embolism are relatively small; however, the relative risks are concerning: 6.0 and 4.8, respectively. Importantly, as noted above, the risk difference for device/shunt thrombosis is considerably underestimated, because the analysis assumes that all patients were on dialysis, which is untrue. (Fortunately, additional estimates of the risk of device/shunt thrombosis are available from studies in the DD patient population, shown later, where all subjects are on dialysis and the denominators are certain.)

Seizure is another serious adverse event of special interest, as seizures are an adverse drug reaction with ESAs. Although the numbers of subjects with serious adverse events of seizure are relatively small, the relative risk of 5.4 merits concern (9 vs. 1 event).

The signal of serious infection was unexpected, but sepsis/septic shock is an obvious concern (risk difference 1.3 per 100 P-Y; estimated relative risk = 2.37), and it is reinforced by signals for serious urinary tract infections, bacterial infections, cellulitis, and peritonitis. Again, as noted above, it is safe to assume that most subjects who reported peritonitis were on peritoneal dialysis. Although the relative risk of peritonitis may be reasonably accurate, the risk difference may be underestimated here.

Other notable serious adverse events include acute kidney injury, hyperkalemia, fracture, gastrointestinal hemorrhage, and hyponatremia.

One might reasonably ask whether some serious adverse events were more common in the placebo groups than in the roxadustat groups. Queries for pulmonary edema, anemia, angina, fatigue, hypotension, and dyspnea favored roxadustat, with event rates exceeding 0.5 per 100 P-Y in the placebo groups ($\geq$ 11 events) and relative risks < 0.75.

Study 610

Unlike the placebo-controlled studies above, Study 610 employed darbepoetin alfa as an active comparator, and time-on-treatment was similar between the two groups. Thus, serious adverse events are expressed as simple percentages, without correction for time-on-study. Of note, the total number of subjects in Study 610 was ~1/7 the number of subjects in the three pooled studies.

Table 19 shows serious adverse events (and queries) where the frequency in the roxadustat group was > 5% and the relative risk vs. darbepoetin alfa exceeded ~1.3. Note: the threshold for inclusion of serious adverse events in this table differed from the threshold for the pooled analyses of Studies 001, 060, and 608; however, they correspond to similar numbers of adverse events in roxadustat-treated groups.

[1] The list of adverse event terms in the query is shown in the appendix.

Signals for both serious thrombosis and infection events are again apparent. The thrombosis difference is particularly important because it is evident when compared here to darbepoetin alfa, which is itself known to predispose to thrombotic events.

Table 19: Serious Adverse Events—Study 610

	Roxadustat N = 323	Darbepoetin alfa N = 293	Risk Difference (%)	Relative Risk
N (%)				
Infection, all	48 (14.9%)	34 (11.6%)	3.3	1.28
Bacterial infectious disorders	18 (5.6%)	7 (2.4%)	3.2	2.33
Pneumonia FDA	19 (5.9%)	12 (4.1%)	1.8	1.44
Thrombosis	20 (6.2%)	13 (4.4%)	1.8	1.41

All listing are queries; FDA = FDA query

One might reasonably question whether there were serious adverse events that occurred at a frequency of 5% in the darbepoetin group with a relative risk favoring *roxadustat*. The frequencies for congestive heart failure (query) were 5.0% and 7.5% in subjects treated with roxadustat and darbepoetin alfa, respectively. No other serious adverse events (or queries) were found that favored roxadustat over darbepoetin alfa.

All Adverse Events

Table 20 lists the results of pooled analyses of adverse events and adverse event queries for the three major studies in the NDD patient population, where the event rate was > 2 per 100 P-Y in the roxadustat groups, and the relative risk (vs. placebo) was > 1.2. This listing of all adverse events includes the serious adverse events described above.

Table 20 is similar to the previous table, with the addition of estimated relative risks for all ascertainment windows. The heights of the vertical violet bars at right represent the estimated relative risks for the OT+7, OT+28, and OT+All (On-Study) analyses, respectively. Thus, the height of the violet bar at left corresponds to the relative risk for the OT+7 analysis, which matches the relative risk in the column 'Relative Risk Based on P-Y.' The center and right violet vertical bars show the results for the OT+28 and on-study analyses. Inspection of the three violet bars for each listing shows how the risk ratios differ across the ascertainment windows. The relative risks are fairly consistent across the OT+7, OT+28, and On-study ascertainment windows for most of these adverse events. Device/shunt thrombosis/occlusion and sepsis/septic shock are exceptions, where the relative risk decreases somewhat for the OT+All ascertainment window.

Again, there are notable signals for thrombotic events, sepsis/septic shock, bacterial infections, seizures, and hyperkalemia. There is a signal for face edema with a small number of events, but a substantial relative risk (8.4). There are signals for insomnia, rash, peripheral edema, acute kidney injury, and fracture; however, the risk differences are small. Peripheral edema and the query 'edema, fluid retention overload' show risk differences around 1 per 100 P-Y range, and are risks of ESAs. Nausea, vomiting, and dyspepsia all have estimated relative risks of 1.2 with risk differences ~1 per 100 P-Y, and the fact that they were detected together suggests drug-relatedness. Malignancy is neutral.

Considering the large number of adverse events and queries examined, it is reasonable to consider whether there are signals that favored *placebo*. The only adverse events reported at a rate > 2 per 100 P-Y in patients who received placebo with a relative risk < 0.8 (i.e., worse in the placebo groups) were anemia, asthenia, fatigue, hypotension, and myocardial ischemia.

Table 20: All Adverse Events—Studies 001, 060, and 608; OT+7, OT+28, and OT+All Ascertainment Windows

	Adverse Events On-treatment (OT) Plus 7 Days						Relative Risk; On-treatment plus 7, 28, 99 Days
	Patients with events (%)		Events (per 100 P-Y)		Risk Difference (per 100 P-Y)	RR Based on P-Y	
	Rox	Pbo	Rox	Pbo			
Numbers of patients ->	2386	1884					
Patient-years ->			3870	2323			
Thombotic Events							
Device/shunt thrombosis, occlusion, malfunction, stenosis #	88 (3.7)	20 (1.1)	2.3	0.9	1.4	2.6	
Device/shunt thrombosis (VAT) #	71 (3)	17 (0.9)	1.8	0.7	1.1	2.5	
Thrombosis #	195 (8.2)	76 (4)	5.0	3.3	1.8	1.5	
Stroke (includes ischemic and hemorrhagic) #	57 (2.4)	29 (1.5)	1.5	1.2	0.2	1.2	
Infections							
Sepsis/septic shock #	100 (4.2)	28 (1.5)	2.6	1.2	1.4	2.1	
Bacterial infectious disorders HLGT #	207 (8.7)	102 (5.4)	5.3	4.4	1.0	1.2	
Nasopharyngitis FDA N #	129 (5.4)	66 (3.5)	3.3	2.8	0.5	1.2	
Laboratory Abnormalities							
Hyperkalemia #	274 (11.5)	134 (7.1)	7.1	5.8	1.3	1.2	
Iron deficiency #	114 (4.8)	49 (2.6)	2.9	2.1	0.8	1.4	
Gastrointestinal							
Nausea FDA N #	242 (10.1)	117 (6.2)	6.3	5.0	1.2	1.2	
Dyspepsia FDA N #	155 (6.5)	76 (4)	4.0	3.3	0.7	1.2	
Vomiting FDA N #	148 (6.2)	75 (4)	3.8	3.2	0.6	1.2	
Decreased appetite (actual term)	97 (4.1)	49 (2.6)	2.5	2.1	0.4	1.2	
Miscellaneous							
Face oedema (actual term)	14 (0.6)	1 (0.1)	0.4	0.0	0.3	8.4	
Seizure FDA N #	24 (1)	3 (0.2)	0.6	0.1	0.5	4.8	
Insomnia FDA N #	131 (5.5)	46 (2.4)	3.4	2.0	1.4	1.7	
Rash FDA N #	110 (4.6)	53 (2.8)	2.8	2.3	0.6	1.2	
Oedema peripheral (actual term)	275 (11.5)	140 (7.4)	7.1	6.0	1.1	1.2	
Acute kidney injury FDA N #	125 (5.2)	63 (3.3)	3.2	2.7	0.5	1.2	
Fracture #	102 (4.3)	52 (2.8)	2.6	2.2	0.4	1.2	
Edema, fluid retention, overload #	515 (21.6)	289 (15.3)	13.3	12.4	0.9	1.1	
Systemic hypertension FDA N*	411 (17.2)	224 (11.9)	10.6	9.6	1.0	1.1	
Malignancy FDA N #	43 (1.8)	34 (1.8)	1.1	1.5	-0.4	0.8	

Listings labeled "actual term" represent individual preferred terms.

All other listings represent queries that combine multiple, related adverse event terms.

"FDA N" = FDA query; P-Y = patient-year; RR = relative risk

Study 610

Table 21 shows all adverse events and adverse event queries that were reported at a frequency of > 5% in the roxadustat group, and > 2% higher than in the darbepoetin alfa group in Study 610. (As previously noted, roxadustat was compared to darbepoetin alfa in this study rather than placebo, and time-on-treatment was similar between the two treatment groups.)

Table 21: All Adverse Events—Study 610

	Roxadustat N = 323	Darbepoetin alfa N = 293	Risk Difference (%)	Relative Risk
N (%)				
Hyperphosphatemia (term)	23 (7.1%)	9 (3.1%)	4.0	2.29
Edema, fluid retention, overload	62 (19.2%)	45 (15.4%)	3.8	1.25
Peripheral edema FDA	45 (13.9%)	35 (11.9%)	2.0	1.17
Insomnia FDA	18 (5.6%)	6 (2%)	3.6	2.80
Muscle spasms (term)	23 (7.1%)	12 (4.1%)	3.0	1.73
Dyspnea FDA	18 (5.6%)	8 (2.7%)	2.9	2.07
Thrombosis	25 (7.7%)	15 (5.1%)	2.6	1.51
Arrhythmia FDA	38 (11.8%)	28 (9.6%)	2.2	1.23
Nausea (term)	26 (8%)	17 (5.8%)	2.2	1.38
Constipation FDA	19 (5.9%)	11 (3.8%)	2.1	1.55
Headache FDA	18 (5.6%)	10 (3.4%)	2.2	1.65
Hypotension FDA	17 (5.3%)	9 (3.1%)	2.2	1.71
Bronchitis (term)	20 (6.2%)	12 (4.1%)	2.1	1.51

Adverse events denoted by "term" are individual preferred terms. All others are queries.
FDA = FDA query

Signals for peripheral edema, edema, fluid retention/overload, insomnia, thrombosis, and nausea have been observed in other studies, and their observation here is reinforcing. In particular, thrombosis and fluid retention/overload are labeled adverse drug reactions for ESAs. Adverse events not heretofore observed include hyperphosphatemia, muscle spasms, dyspnea, arrhythmia, constipation, headache, hypotension, and bronchitis. Analyses of adverse events in the DD patient population will provide a far more robust comparison between roxadustat and darbepoetin alfa.

DD Patient Population

The DD patient population includes 3880 randomized subjects who received ≥ 1 dose of study drug in the three major randomized, double-blind, active-controlled studies (002, 063, 064). Study 063 enrolled subjects who had initiated dialysis within 4 months of randomization. Studies 002 and 064 enrolled such subjects, as well as subjects who had been stable on dialysis and were using an ESA. Subjects were randomized to roxadustat or epoetin alfa. Analyses are shown separately for Study 613, which was conducted in Europe and included randomization to either roxadustat or darbepoetin alfa. Because ESAs were used as active controls for these trials, the adverse event tables include most of the adverse drug reactions currently in the ESA labels.

Deaths

Table 22 provides a tabulation of adjudicated deaths in the DD patient population, with numbers compiled from the applicant's table. There is a slight trend toward a higher rate of death in patients who received roxadustat vs. epoetin alfa. The risk difference was 0.62 deaths per 100 P-Y, with a relative risk of 1.08. Slightly more than half the deaths were cardiovascular in nature. The leading causes of cardiovascular death (and the largest contributors to the risk difference) were acute MI and sudden cardiac death. The leading non-cardiovascular causes of death were infection and "renal" deaths. Deaths will be discussed in greater detail in the MACE section.

Table 22: Adjudicated Causes of Death—Studies 002, 063, 064; Ascertainment Window OT+28

	Patients with events (%)		Events (per 100 PY)		Risk Difference (per 100 P-Y)	Relative Risk Based on P-Y
	Roxadustat	Epoetin alfa	Roxadustat	Epoetin alfa		
	N = 1940	N = 1940	3447 P-Y	3874 P-Y		
Total Deaths	282 (14.54)	293 (15.1)	8.18	7.56	0.62	1.08
Cardiovascular-related	159 (8.2)	160 (8.25)	4.61	4.13	0.48	1.12
Sudden cardiac death	86 (4.43)	85 (4.38)	2.50	2.19	0.31	1.14
Acute MI	26 (1.34)	16 (0.82)	0.75	0.41	0.34	1.83
Heart failure	20 (1.03)	17 (0.88)	0.6	0.4	0.14	1.32
Stroke	14 (0.72)	25 (1.29)	0.41	0.65	-0.24	0.63
Other cardiovascular	7 (0.36)	7 (0.36)	0.20	0.18	0.02	1.12
Non-cardiovascular-related	101 (5.21)	102 (5.26)	2.93	2.63	0.30	1.11
Infection	47 (2.42)	46 (2.37)	1.36	1.19	0.17	1.15
Renal	15 (0.77)	10 (0.52)	0.44	0.26	0.18	1.69
Hemorrhage	7 (0.36)	5 (0.26)	0.20	0.13	0.07	1.57
Gastrointestinal	5 (0.26)	10 (0.52)	0.15	0.26	-0.11	0.56
Malignancy	5 (0.26)	7 (0.36)	0.15	0.18	-0.03	0.80
Undetermined	22 (1.13)	31 (1.6)	0.64	0.80	-0.16	0.80

Data are compliled from Table 117 in the applicant's Integrated Summary of Safety; P-Y = patient-year

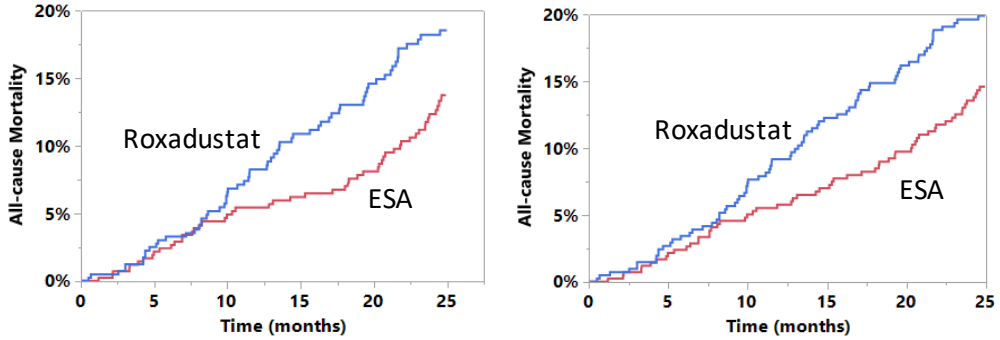
Deaths in Study 613

Study 613 was a European study that randomized stable DD subjects 1:1 to roxadustat (N = 414) or ESA (N = 420). According to the applicant, within the OT+28 ascertainment window, there were 64 (9.7 per 100 P-Y) and 51 (6.8 per 100 P-Y) all-cause deaths in the roxadustat and ESA treatment groups, respectively. The applicant's estimated HR is 1.588 (95% CI 1.096, 2.300); P = 0.015. The risk difference is 2.9 deaths per 100 P-Y.

For the On-study analysis, there were 78 (10.6 per 100 P-Y) vs. 59 (7.4 per 100 P-Y) deaths for the roxadustat and ESA groups, respectively. The applicant's estimated HR was 1.562 (95% CI 1.112, 2.195); p = 0.010. The risk difference is 3.2 deaths per 100 P-Y.

Kaplan-Meier survival curves are shown for the OT+28 and On-study analyses in Figure 4, left, and right. In accord with the applicant's analyses, the log-rank p-values are nominally statistically significant in these unadjusted Kaplan-Meier analyses. Causes of death were not adjudicated, and no predominant causes were apparent based on the preferred terms of adverse events that were cited as leading to death.

Figure 4: Kaplan-Meier Curves for Time to Death—Study 613, OT+28 (left); On-study (right)



Serious Adverse Events

Table 23 shows the serious adverse events and serious adverse event queries for the pooled studies in the DD patient population (OT + 7 ascertainment window). Events and queries are shown for those where the event rate (per 100 P-Y) is ≥ 0.5 and the relative risk ≥ 1.3, along with adverse drug reactions from the ESA labeling.

Table 23: Serious Adverse Events—Studies 002, 063, and 064; OT+7 Ascertainment Window

	Patients with Events N (%)		Events (per 100 PY)		Absolute Δ Risk (per 100 P-Y)	Relative Risk Based on P-Y
	Roxadustat	ESA	Roxadustat	ESA		
	N = 1940	N = 1940	3315 P-Y	3744 P-Y		
Thombotic Events						
Thrombosis	241 (12.42)	201 (10.36)	7.27	5.37	1.90	1.4
Device/shunt thrombosis	121 (6.24)	94 (4.85)	3.65	2.51	1.14	1.5
Deep vein thrombosis (term)	24 (1.24)	7 (0.36)	0.72	0.19	0.53	3.9
Miscellaneous						
Hypoglycemia FDA	29 (1.49)	25 (1.29)	0.87	0.67	0.20	1.3
Gastroenteritis	27 (1.39)	16 (0.82)	0.81	0.43	0.38	1.9
Seizure FDA	26 (1.34)	19 (0.98)	0.78	0.51	0.27	1.6
Pancreatitis FDA	20 (1.03)	11 (0.57)	0.60	0.29	0.31	2.1
Adverse Drug Reactions Known for ESAs						
Systemic hypertension FDA	89 (4.59)	110 (5.67)	2.68	2.94	-0.26	0.9
Myocardial infarction FDA	88 (4.54)	85 (4.38)	2.65	2.27	0.38	1.2
Infusion site reaction (term)	0 (0)	0 (0)	0.00	0.00	0.00	-
Injection site reaction (term)	0 (0)	0 (0)	0.00	0.00	0.00	-
Bronchospasm FDA	7 (0.36)	4 (0.21)	0.21	0.11	0.10	2.0
Toxic epidermal necrolysis (term)	0 (0)	1 (0.05)	0.00	0.03	-0.03	0.0
Stevens-Johnson syndrome (term)	1 (0.05)	(0)	0.03	0.00	0.03	-
Dyspnea FDA	11 (0.57)	17 (0.88)	0.33	0.45	-0.12	0.7
Peripheral edema FDA	5 (0.26)	2 (0.1)	0.15	0.05	0.10	2.8
Edema, fluid retention/overload	76 (3.92)	76 (3.92)	2.29	2.03	0.26	1.1
Angina	27 (1.39)	30 (1.55)	0.81	0.80	0.01	1.0
Rash FDA	2 (0.1)	2 (0.1)	0.06	0.05	0.01	1.1

All listed adverse events are queries except those denoted by "term," which are individual preferred terms.
FDA = FDA query; P-Y = patient-year

Serious thrombotic events and seizures are again prominent. In the NDD patient population, they were detected against a placebo background; importantly, here they are evident even against epoetin alfa, which is itself known to pose these risks. Other signals of concern include serious adverse events of hypoglycemia, gastroenteritis, and pancreatitis.

Many of the adverse drug reactions known for ESAs (Table 23, bottom) are low in frequency and the results are uninterpretable. For the more frequent serious adverse events that are listed as adverse drug reactions for ESAs (e.g., systemic hypertension and edema, fluid retention/overload), event rates with roxadustat are similar to those for epoetin alfa, which would support including them in roxadustat's labeling if the drug is approved. For MI, the relative risk is 1.2. Myocardial infarction will be discussed in detail in the MACE section.

Study 613

Table 24 shows the serious adverse events in that occurred at a frequency > 5% in the roxadustat group with a relative risk (vs. ESAs) that exceeded 1.3. As has been mentioned previously, thrombosis of vascular access is listed as an adverse drug reaction in the ESA labeling (as a warning). The risk of congestive heart failure is also listed as an adverse drug reaction when ESAs are used to target excessive Hb concentrations. Thus, these signals from Study 613 are quite concerning (both with a relative risk of 2 vs. ESAs), because they suggest that roxadustat's risks are even greater than those of ESAs. Moreover, serious bacterial infections were more frequent with roxadustat than with the ESAs, also as noted in studies in the NDD patient population where roxadustat was compared to placebo. Serious adverse events consistent with other adverse drug reactions from the ESA label were infrequent (not shown).

Table 24: Serious Adverse Events—Study 613

N (%)	Roxadustat N = 414	ESA N = 420	Risk Difference (%)	Relative Risk
Congestive heart failure	31 (7.5%)	16 (3.8%)	3.7	2.0
Arteriovenous fistula thrombosis (term)	29 (7%)	15 (3.6%)	3.4	2.0
Device/shunt thrombosis	35 (8.5%)	22 (5.2%)	3.3	1.6
Bacterial infectious disorders	23 (5.6%)	16 (3.8%)	1.8	1.5
Thrombosis	52 (12.6%)	43 (10.2%)	2.4	1.2

All listed adverse events are queries except those denoted by "term," which are individual preferred terms.

All Adverse Events

Table 25 lists all adverse events in the three principal studies in the DD patient population where the adverse event rate was > 2 per 100 P-Y and the relative risk (vs. ESAs) exceeded 1.3. The OT+7 ascertainment window was used; however, results were essentially the same when analyzed with the OT+28 and OT+All windows (data not shown). The listings at the bottom of the table show the adverse events that correspond to adverse drug reactions in the ESA labeling.

Roxadustat shows a strong thrombosis signal here, even when compared to epoetin alfa, a drug for which thrombosis is a labeled adverse drug reaction. With 91% of study subjects on hemodialysis, the rates of device/shunt thrombosis (vascular access thrombosis) are approximately 8.2 and 6.1 per 100 P-Y for roxadustat and epoetin alfa, for a risk difference of 2.1 per 100 P-Y and a relative risk of 1.3. Note that this comparison is based on a large number of adverse events: 271 vs. 228 in the roxadustat and epoetin alfa groups, respectively. Deep vein thrombosis is infrequent (29 vs. 19 events), but the relative risk is 1.7. Vomiting appears here and also appears as a risk in the NDD patient population.

Among the adverse events that correspond to adverse drug reactions in the ESA labeling, the signals for rash, malignancy, MI, peripheral edema, and hypertension are most prominent. In fact, all of the adverse events that correspond with the adverse drug reactions of ESAs show relative risks near or above unity (Stevens-Johnson syndrome and toxic epidermal necrolysis excepted; they are rare). Based on these data, the adverse drug reactions in the ESA labeling should convey to the labeling of roxadustat, if approved.

Table 25: All Adverse Events—Studies 002, 063, 064; OT+7 Ascertainment Window

	Events, N (%)		Events (per 100 PY)		Risk Difference (per 100 P-Y)	Relative Risk Based on P-Y
	Roxadustat	Epoetin alfa	Roxadustat	Epoetin alfa		
	N = 1940	N = 1940	3315 P-Y	3744 P-Y		
Thombotic Events						
Device/shunt thrombosis/ occlusion/malfunction/stenosis	319 (16.44)	276 (14.23)	9.62	7.37	2.25	1.31
Device/shunt thrombosis	271 (13.97)	228 (11.75)	8.17	6.09	2.08	1.34
Thrombosis	392 (20.21)	344 (17.73)	11.82	9.19	2.63	1.29
Deep vein thrombosis (term)	29 (1.49)	19 (0.98)	0.87	0.51	0.36	1.72
Gastrointestinal						
Vomiting FDA	161 (8.3)	134 (6.91)	4.86	3.58	1.28	1.36
Gastroenteritis	86 (4.43)	68 (3.51)	2.59	1.82	0.77	1.43
Miscellaneous						
Headache FDA	198 (10.21)	157 (8.09)	5.97	4.19	1.78	1.42
Hypotension FDA	230 (11.86)	199 (10.26)	6.94	5.32	1.62	1.31
Fatigue FDA	115 (5.93)	97 (5)	3.47	2.59	0.88	1.34
Pruritus FDA	103 (5.31)	85 (4.38)	3.11	2.27	0.84	1.37
Muscle spasms (term)	107 (5.52)	92 (4.74)	3.23	2.46	0.77	1.31
Hypoglycemia FDA	79 (4.07)	70 (3.61)	2.38	1.87	0.51	1.27
Tachycardia FDA	73 (3.76)	60 (3.09)	2.20	1.60	0.60	1.37
Adverse Drug Reactions Known for ESAs						
Systemic hypertension FDA	365 (18.81)	367 (18.92)	11.01	9.80	1.21	1.12
Edema, fluid retention, overload	234 (12.06)	260 (13.4)	7.06	6.95	0.11	1.02
Dyspnea FDA	129 (6.65)	150 (7.73)	3.89	4.01	-0.12	0.97
Peripheral edema FDA	98 (5.05)	95 (4.9)	2.96	2.54	0.42	1.16
Myocardial infarction FDA	91 (4.69)	87 (4.48)	2.74	2.32	0.42	1.18
Rash FDA	67 (3.45)	53 (2.73)	2.02	1.42	0.60	1.43
Angina	50 (2.58)	76 (3.92)	1.51	2.03	-0.52	0.74
Bronchospasm FDA	13 (0.67)	18 (0.93)	0.39	0.48	-0.09	0.82
Angioedema FDA	4 (0.21)	5 (0.26)	0.12	0.13	-0.01	0.90
Anaphylactic reaction FDA	3 (0.15)	4 (0.21)	0.09	0.11	-0.02	0.85
Injection site reaction	2 (0.1)	2 (0.1)	0.06	0.05	0.01	1.13
Infusion site reaction, reaction	1 (0.05)	7 (0.36)	0.03	0.19	-0.16	0.16
Stevens-Johnson syndrome (term)	1 (0.05)	0 (0)	0.03	0.00	0.03	-
Toxic epidermal necrolysis (term)	0 (0)	1 (0.05)	0.00	0.03	-0.03	0.00
Malignancy FDA	38 (1.96)	36 (1.86)	1.15	0.96	0.19	1.19
Seizure FDA	45 (2.32)	33 (1.7)	1.36	0.88	0.48	1.54

Adverse events denoted by "term" are individual preferred terms. All others are queries.
FDA = FDA query; P-Y = patient-year

Study 613

Table 26 shows the adverse events in that occurred at a frequency > 5% in the roxadustat group with a relative risk (vs. ESAs) that exceeded 1.3, as well as other significant adverse events. The thrombotic adverse events are once again prominent, even against the background of ESAs. (Of note, there are only a few strokes and MIs, and these favor the roxadustat group over the ESA group.) Signals for nausea and congestive heart failure are also obvious, and have been observed in other trials. With respect to the adverse events that correspond to adverse drug reactions in the ESA labels, the only adverse event with a significant number of events is systemic hypertension, which slightly favors roxadustat vs. ESAs.

Table 26: All Adverse Events—Study 613

N (%)	Roxadustat N = 414	ESA N = 420	Risk Difference (%)	Relative Risk
Thrombotic Events				
Thrombosis	77 (18.6%)	65 (15.5%)	3.10	1.2
Deep vein thrombosis (term)	6 (1.4%)	0 (0%)	1.40	-
Pulmonary embolism (term)	4 (1%)	2 (0.5%)	0.50	2.0
Device/shunt thrombosis	64 (15.5%)	45 (10.7%)	4.80	1.4
Arteriovenous fistula thrombosis (term)	50 (12.1%)	31 (7.4%)	4.70	1.6
Myocardial infarction FDA	10 (2.4%)	17 (4%)	-1.60	0.6
Ischemic stroke	1 (0.2%)	6 (1.4%)	-1.20	0.2
Miscellaneous				
AV fistula thrombosis/occlusion/ malfunction/stenosis	71 (17.1%)	57 (13.6%)	3.50	1.3
Nausea FDA	30 (7.2%)	8 (1.9%)	5.30	3.8
Congestive heart failure	34 (8.2%)	20 (4.8%)	3.40	1.7
Pruritus FDA	25 (6%)	12 (2.9%)	3.10	2.1
Dizziness FDA	25 (6%)	17 (4%)	2.00	1.5
Adverse Drug Reactions Known for ESAs			0.00	-
Systemic hypertension FDA	79 (19.1%)	85 (20.2%)	-1.10	0.9
Edema, fluid retention, overload	18 (4.3%)	23 (5.5%)	-1.20	0.8
Dyspnea FDA	16 (3.9%)	15 (3.6%)	0.30	1.1
Myocardial infarction FDA	10 (2.4%)	17 (4%)	-1.60	0.6
Peripheral edema FDA	10 (2.4%)	9 (2.1%)	0.30	1.1
Rash FDA	9 (2.2%)	11 (2.6%)	-0.40	0.8
Angina	8 (1.9%)	12 (2.9%)	-1.00	0.7
Bronchospasm FDA	1 (0.2%)	1 (0.2%)	0.00	1.0
Toxic epidermal necrolysis	1 (0.2%)	0 (0%)	0.20	-
Infusion site reaction	0 (0%)	0 (0%)	0.00	-
Injection site reaction	0 (0%)	0 (0%)	0.00	-
Stevens-Johnson syndrome	0 (0%)	0 (0%)	0.00	-

All listed adverse events are queries except those denoted by "term," which are individual preferred terms. FDA = FDA query

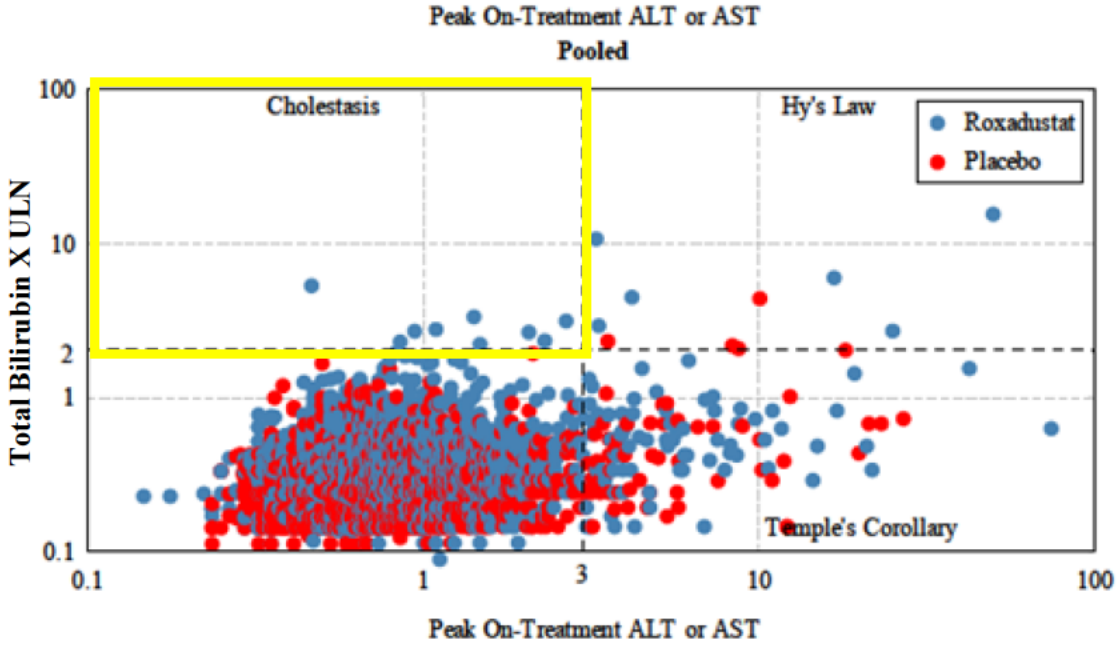
Laboratory Findings

Laboratory findings were analyzed separately for the NDD and DD patient populations. The only important finding was related to abnormal hepatic laboratory values. We obtained expert consultation from the Division of Hepatology and Nutrition, who conferred with the Office of Surveillance and Epidemiology.

NDD population

Figure 5 is a standard eDISH scatterplot of total bilirubin (x upper limit of normal [ULN]) by peak alanine aminotransferase (ALT) or aspartate aminotransferase (AST) (x ULN) for the three principal studies in the NDD population. There were nine cases of increased total and direct bilirubinemia in the roxadustat treatment arms, vs. none in placebo (left upper cholestasis quadrant, yellow highlighted area). Few appeared in the right upper quadrant of the cholestatic scatterplot (data not shown), indicating that most of these jaundiced, cholestatic cases did not have significant elevations in alkaline phosphatase (AP). There was also a modest overall shift in patients in the roxadustat arm toward the upper right part of the eDISH plot (higher ALT/AST, higher bilirubin).

Figure 5: NDD population—Plot of Hepatocellular Injury (Total Bilirubin vs. ALT or AST)



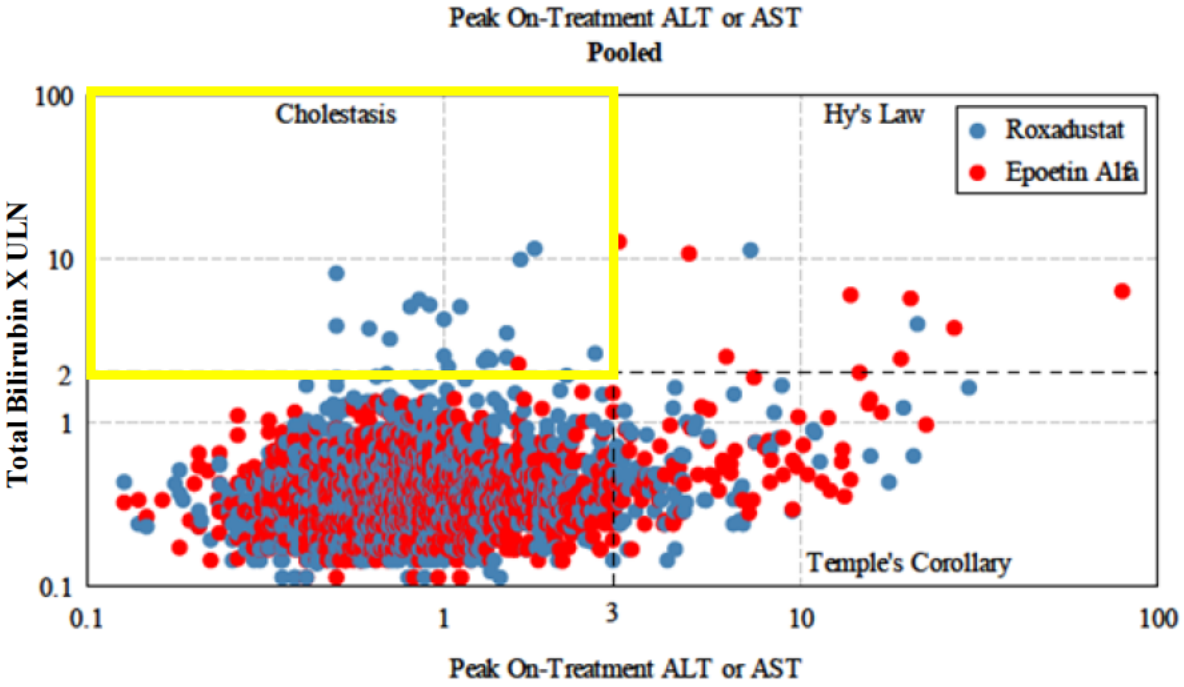
DD population

The eDISH scatterplot (Figure 6) does not show the same general shift in roxadustat-treated patients toward the upper right quadrant as was observed in the NDD trials. With equal randomization to roxadustat or epoetin alfa, there tend to be fewer roxadustat-treated patients in the Hy's Law and Temple's Corollary quadrants.

As was observed in the NDD studies, however, in the left upper cholestasis quadrant (yellow highlighted area) there are 19 roxadustat-treated subjects vs. 1 in epoetin alfa-treated subject. Few subjects

appeared in the right upper quadrant of the cholestatic scatterplot (data not shown). These findings also suggest direct hyperbilirubinemia, not accompanied by significant AP elevations.

Figure 6: DD population—Plot of Hepatocellular Injury (Total Bilirubin vs. ALT or AST)



For both the NDD and DD patient populations, our experts reviewed narratives and clinical details on all patients with important abnormalities in liver tests, and found a total of 19 patients of potential concern for severe DILI with jaundice, either cholestatic, hepatocellular, or mixed pattern. They assessed all cases as unlikely to represent liver injury due to roxadustat. All had a more likely competing diagnosis (e.g., sepsis, gallstone disease, shock liver, congestive hepatopathy, acute viral hepatitis), latency inconsistent with DILI, or resolution despite continuation of drug and/or negative re-challenge.

In summary, roxadustat may cause bland cholestasis (elevated bilirubin without significant elevation in hepatic transaminases), but no significant hepatocellular injury. For the overall NDD and DD populations, there were 19 cases in 4326 roxadustat-treated subjects, i.e., a rate of 0.44%. There were no Hy's Law cases; indeed, careful analysis of all suspicious cases revealed no cases of obvious DILI.

Bland cholestasis generally carries a good prognosis if the inciting event is resolved or the drug is held. Examples of drugs that cause DILI-related bland cholestasis include estrogens and androgens. The recommendation from our consultants was that bland cholestasis would not merit a Warning in labeling; however, for elevations of bilirubin/AP, the drug should be held until resolution, absent clear evidence of another cause, e.g., sepsis.

Analysis of MACE

NDD Patient Population

The objective of the NDD MACE assessment was to demonstrate non-inferiority of roxadustat compared with placebo with respect to cardiovascular risk, based on a meta-analysis of the three principal phase 3

randomized, placebo-controlled trials (001, 060, 608). As noted above, MACE was a composite endpoint that included MI, stroke, and all-cause mortality. Study endpoints were adjudicated by an independent clinical endpoint committee, whose members were blinded to treatment assignment.

The FDA did not agree prospectively on a risk margin and did not agree on the interpretation of the results using strictly a non-inferiority hypothesis testing approach. As such, our interpretation focuses on the estimation of the MACE risk and the uncertainty around it (95% confidence interval) in the NDD patient population.

The MACE meta-analysis included pre-specified, trial-specific stratification factors. The applicant also provided results using common stratification factors defined post hoc. The findings were qualitatively similar, regardless of the stratification factors.

Event Ascertainment Window: The ascertainment window for the primary analysis included the entire study duration, regardless of treatment exposure after randomization, referred to as the On-study analysis. An analysis using the OT+7 ascertainment window was conducted as a sensitivity analysis.

Analysis Model: For each trial, Cox regression was used to model the treatment effect (roxadustat vs. placebo), stratified by baseline Hb values (< 8 g/dL vs. ≥ 8 g/dL); history of cardiovascular, cerebrovascular, or thromboembolic diseases (yes vs. no); baseline eGFR (< 30 vs. ≥ 30); and geographic region (US vs. others for Studies 001 and 608; Western Europe vs. others for Study 608). Hazard ratios from each trial were combined using weights inversely proportional to the variance of the study-specific log HR estimates, thereby providing an overall estimate of the HR and its uncertainty (95% CI). This approach preserves the randomization of each trial and avoids a naïve assumption that the patient samples in each trial are exchangeable.

MACE Composite Endpoint—NDD Population: Results for time to first MACE for both the on-study and OT+7 analyses are shown in Table 27.

Table 27: Summary of MACE Analysis Results in the NDD Population

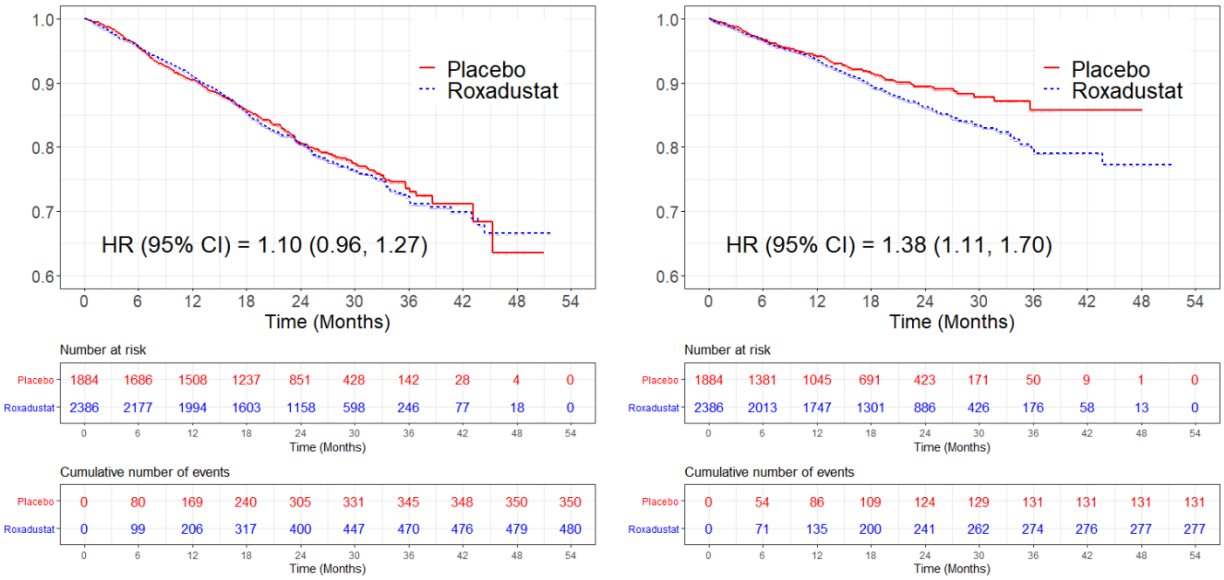
	On-study Analysis (Primary)			OT+7 Analysis (Sensitivity)	
	Roxadustat N = 2386 PY = 4509.6	Placebo N = 1884 PY = 3406.2		Roxadustat N = 2386 PY = 3843.2	Placebo N = 1884 PY = 2331.6
Events (rate)	480 (10.6)	350 (10.3)		277 (7.2)	131 (5.6)
HR (95% CI)	1.10 (0.96, 1.27)			1.38 (1.11, 1.70)	

There is a considerable difference between the estimated HRs for the primary On-study analysis and the OT+7 sensitivity analyses, with HRs (95% CI) of 1.10 (0.96, 1.27) and 1.38 (1.11, 1.70), respectively. Whereas the results seem reassuring for the On-study analysis, the lower limit of the 95% CI for the OT+7 sensitivity analysis (1.11) excludes 1.0. Although the exclusion of 1 in the OT+7 analysis merits concern, the differential exposure between roxadustat and placebo complicates the interpretation of the OT+7 analysis in isolation, as this may not represent a fair randomized comparison. For example, subjects who discontinue treatment early (higher in placebo than roxadustat) are censored at the point of treatment discontinuation. In a population in which MACE occurs at a rate > 5 per 100 PY, because subjects in the roxadustat arm are exposed to treatment for a longer duration, they are at risk for a

longer period of time. Thus, the differential dropout may contribute to a biased estimate of the treatment effect in the OT+7 analysis that disfavors roxadustat.

Figure 7 shows the Kaplan-Meier survival curves for MACE. Of note, the OT+7 analysis includes ~22% less follow-up time than the On-study analysis. Event rates (roxadustat vs. placebo) were 10.6 and 10.3 per 100 P-Y in the On-Study analysis, and 7.2 and 5.6 per 100 P-Y in the OT+7 analysis. Many events occurred beyond the 7-day post-treatment window of the OT+7 analysis, with disproportionately more events in the placebo group, especially for all-cause death.

Figure 7: Time to First MACE— On-study Analysis (Left); OT+7 Analysis (Right)



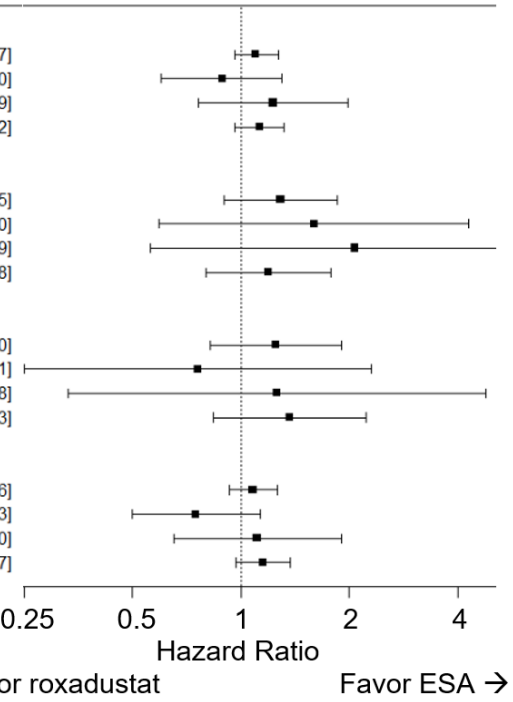
Source: FDA analysis.

MACE results are shown graphically by study, as well as by its components, for the On-study analysis (Figure 8) and the OT+7 analysis (Figure 9).[2] For the On-study analysis where the overall estimated HR for MACE is 1.10, there are trends for increased stroke, and particularly increased MI, in the roxadustat treatment groups (Figure 8). For the OT+7 analysis where the overall estimated HR for MACE is 1.38, there is a nominally statistically significant finding for all-cause mortality (not favoring roxadustat), which is driven by the Study 001, the largest study (Figure 9). There are also trends for higher rates of stroke and MI for roxadustat, and these trends are fairly consistent across the three studies.

[2] Note that for this composite endpoint, the sums of the individual component events do not equal the total numbers of first MACE.

Figure 8: MACE and its Components for Studies in the NDD Population (On-study Analysis)

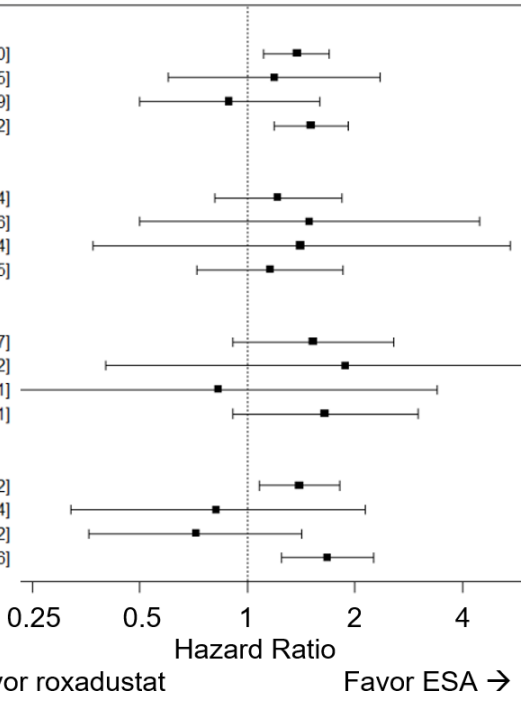
	Number of Events/ PY/ Rate		
	Roxadustat (N = 2,386)	Placebo (N = 1,884)	HR [95% CI]
MACE			
All Studies	480/ 4510/ 10.6	350/ 3406/ 10.3	1.10 [0.96, 1.27]
060	87/ 1277/ 6.8	39/ 536/ 7.3	0.89 [0.60, 1.30]
608	61/ 534/ 11.4	24/ 258/ 9.3	1.23 [0.76, 1.99]
001	332/ 2699/ 12.3	287/ 2612/ 11.0	1.13 [0.96, 1.32]
Myocardial Infarction			
All Studies	86/ 4521/ 1.9	52/ 3396/ 1.5	1.29 [0.90, 1.85]
060	21/ 1277/ 1.6	5/ 531/ 0.9	1.60 [0.59, 4.30]
608	11/ 536/ 2.1	3/ 260/ 1.2	2.07 [0.56, 7.69]
001	54/ 2708/ 2.0	44/ 2605/ 1.7	1.19 [0.80, 1.78]
Stroke			
All Studies	56/ 4546/ 1.2	36/ 3411/ 1.1	1.25 [0.82, 1.90]
060	9/ 1285/ 0.7	5/ 531/ 0.9	0.76 [0.25, 2.31]
608	8/ 540/ 1.5	3/ 260/ 1.2	1.26 [0.33, 4.78]
001	39/ 2721/ 1.4	28/ 2620/ 1.1	1.37 [0.84, 2.23]
All-cause Mortality			
All Studies	400/ 4798/ 8.3	301/ 3721/ 8.1	1.08 [0.93, 1.26]
060	70/ 1308/ 5.4	36/ 541/ 6.7	0.75 [0.50, 1.13]
608	46/ 546/ 8.4	20/ 262/ 7.6	1.11 [0.65, 1.90]
001	284/ 2944/ 9.6	245/ 2919/ 8.4	1.15 [0.97, 1.37]



Source: FDA Analysis

Figure 9: MACE and its Components for Studies in the NDD Population (OT+7 Analysis)

	Number of Events/ PY/ Rate		
	Roxadustat (N = 2,386)	Placebo (N = 1,884)	HR [95% CI]
MACE			
All Studies	277/ 3843/ 7.2	131/ 2332/ 5.6	1.38 [1.11, 1.70]
060	40/ 1124/ 3.6	11/ 382/ 2.9	1.19 [0.60, 2.35]
608	40/ 470/ 8.5	18/ 201/ 9.0	0.89 [0.50, 1.59]
001	197/ 2249/ 8.8	102/ 1749/ 5.8	1.51 [1.19, 1.92]
Myocardial Infarction			
All Studies	72/ 3869/ 1.9	37/ 2340/ 1.6	1.22 [0.81, 1.84]
060	18/ 1133/ 1.6	4/ 382/ 1.0	1.49 [0.50, 4.46]
608	11/ 473/ 2.3	3/ 201/ 1.5	1.41 [0.37, 5.44]
001	43/ 2264/ 1.9	30/ 1757/ 1.7	1.16 [0.72, 1.85]
Stroke			
All Studies	48/ 3888/ 1.2	21/ 2350/ 0.9	1.53 [0.91, 2.57]
060	9/ 1138/ 0.8	2/ 383/ 0.5	1.88 [0.40, 8.82]
608	6/ 477/ 1.3	3/ 202/ 1.5	0.83 [0.20, 3.41]
001	33/ 2273/ 1.5	16/ 1765/ 0.9	1.65 [0.91, 3.01]
All-cause Mortality			
All Studies	183/ 3914/ 4.7	85/ 2358/ 3.6	1.40 [1.08, 1.82]
060	18/ 1146/ 1.6	6/ 383/ 1.6	0.82 [0.32, 2.14]
608	24/ 480/ 5.0	14/ 202/ 6.9	0.72 [0.36, 1.42]
001	141/ 2287/ 6.2	65/ 1773/ 3.7	1.68 [1.25, 2.26]



Source: FDA analysis

MACE in Study 610

Study 610 compared roxadustat to darbepoetin alfa, rather than a placebo. Results for time to first MACE are shown in Table 28 for the On-study and OT+7 approaches. For both analyses, the estimated HRs tended to favor roxadustat over darbepoetin alfa; however, the results were not statistically significant.

Table 28: Summary of MACE Results in Study 610

	On-study Analysis			OT+7 Analysis	
	Roxadustat N = 323 PY = 575.7	Darbepoetin alfa N = 293 PY = 522.6		Roxadustat N = 323 PY = 517.7	Darbepoetin alfa N = 293 PY = 477.1
Events (rate per 100 P-Y)	49 (8.5)	48 (9.2)		31 (6.0)	39 (8.2)
HR (95% CI)	0.89 (0.60, 1.33)			0.70 (0.44, 1.12)	

PY = patient years; OT+7 = On-treatment + 7 days analysis

DD Patient Population:

The objective of the MACE assessment in the DD population was to demonstrate non-inferiority of roxadustat to ESA, based on a meta-analysis of the three principal, phase 3, randomized, ESA-controlled trials (002, 063, 064). MACE was defined as it was for the NDD Population: the composite of all-cause mortality, MI, and stroke, and study endpoints were adjudicated by a blinded, independent clinical endpoint committee. The FDA did not agree prospectively on a risk margin using strictly a non-inferiority hypothesis testing approach. As such, our interpretation focuses on the estimation of the MACE risk and the uncertainty around it (95% CI) in the DD patient population. The primary analysis of MACE was based on the meta-analysis using pre-specified, trial-specific stratification factors.

Event Ascertainment Window: Two ascertainment windows were pre-specified in the protocol. The window of event ascertainment for the primary analysis was to include MACE that occurred after the first dose date and within 7 days after the last dose of study drug, or until the first dose of another anemia drug other than the randomized treatment. This is referred to as the OT+7 analysis.

As a sensitivity analysis, an On-study analysis was conducted that included events occurring during the study regardless of the treatment exposure after randomization.

Analysis Model: For each trial, Cox regression was used to model the treatment effect (roxadustat vs. ESA), stratified by geographic region (US vs. non-US); history of cardiovascular, cerebrovascular, or thromboembolic diseases (yes vs. no); screening Hb values ($\leq$ 8 g/dL vs. > 8 g/dL for Study 063; $\leq$ 10.5 g/dL vs. > 10.5 g/dL for Studies 064 and 002); average prescribed weekly ESA dose in the 4 weeks prior to randomization (epoetin alfa dose, or equivalent epoetin alfa dose for patients on non-epoetin alfa ESA at baseline, of $\leq$ 150 vs. > 150 IU/kg/week for Study 064; not included as a stratification variable for Studies 063 and 002); and incident vs. stable dialysis (dialysis duration $\leq$ 4 months vs. > 4 months for Study 002; not included as stratification variable for Studies 063 and 064). HRs were estimated for each study and then combined using weights inversely proportional to the variance of the study-specific log HR estimates to provide an overall estimate of the HR and its uncertainty (95% CI).

On-treatment Analysis Result (Primary Analysis): Comparing roxadustat to epoetin alfa, the estimated HR (95% CI) for time to first MACE event was 1.02 (0.88, 1.20), i.e., neutral (Table 29). There were 306

and 339 subjects with MACE in the roxadustat and ESA groups, respectively, with follow-up time-adjusted incidence rates of 9.4 and 9.3 per 100 P-Y.

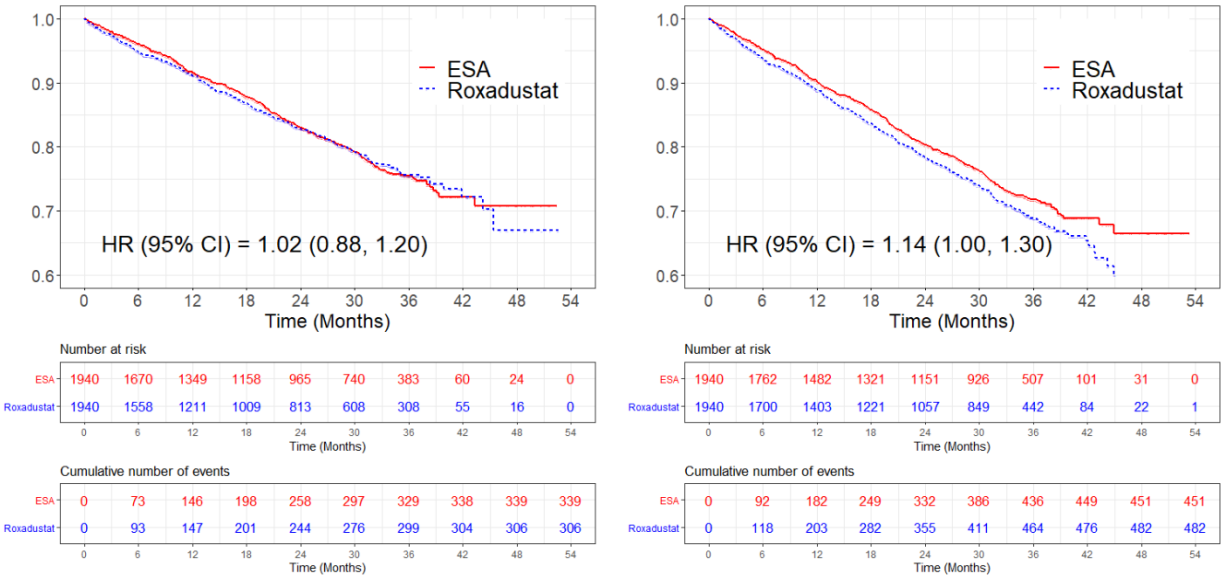
On-study Analysis Result (Sensitivity Analysis): The estimated HR (95% CI) for time to first MACE event was 1.14 (1.00, 1.30), such that the difference was nearly statistically significant (Table 29). There were 482 and 451 subjects with MACE in the roxadustat and ESA groups, respectively, with follow-up time-adjusted incidence rates of 12.4 and 10.9 per 100 P-Y. The HR was driven by differences in all-cause mortality and MI; stroke was neutral.

Table 29: Summary of MACE Analysis Results in the DD Population

	OT+7 Analysis (Primary)			On-Study Analysis (Sensitivity)	
	Roxadustat N = 1940 PY = 3261.2	ESA N = 1940 PY = 3660.3		Roxadustat N = 1940 PY = 3898.9	ESA N = 1940 PY = 4151.0
Events (rate per 100 P-Y)	306 (9.4)	339 (9.3)		482 (12.4)	451 (10.9)
HR (95% CI)	1.02 (0.88, 1.20)			1.14 (1.00, 1.30)	

Kaplan-Meier plots for time to first MACE are shown for the OT+7 and On-study analyses in Figure 10.

Figure 10: Time to First MACE—OT+7 Analysis (Left); On-study Analysis (Right)

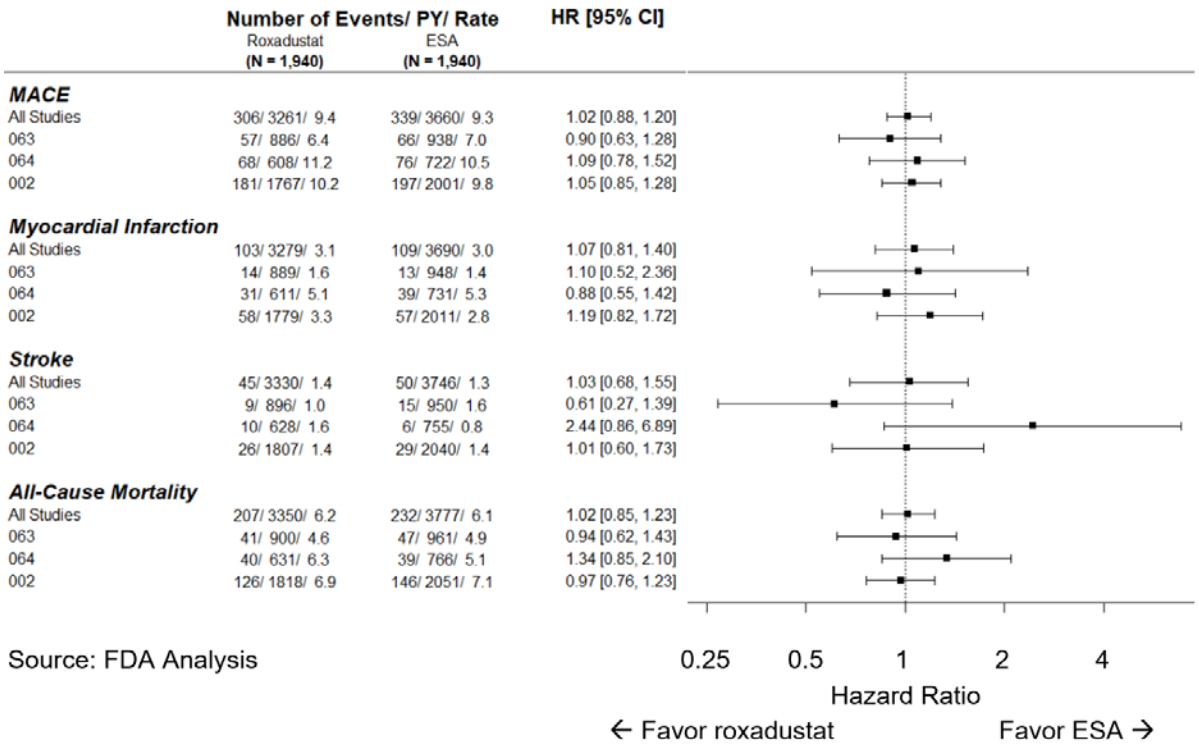


Source: FDA analysis.

Figure 11 and Figure 12 show the results by MACE component and by study for the OT+7 and On-study analyses, respectively.[3] The study-specific estimates and confidence intervals are illustrated for comparison.

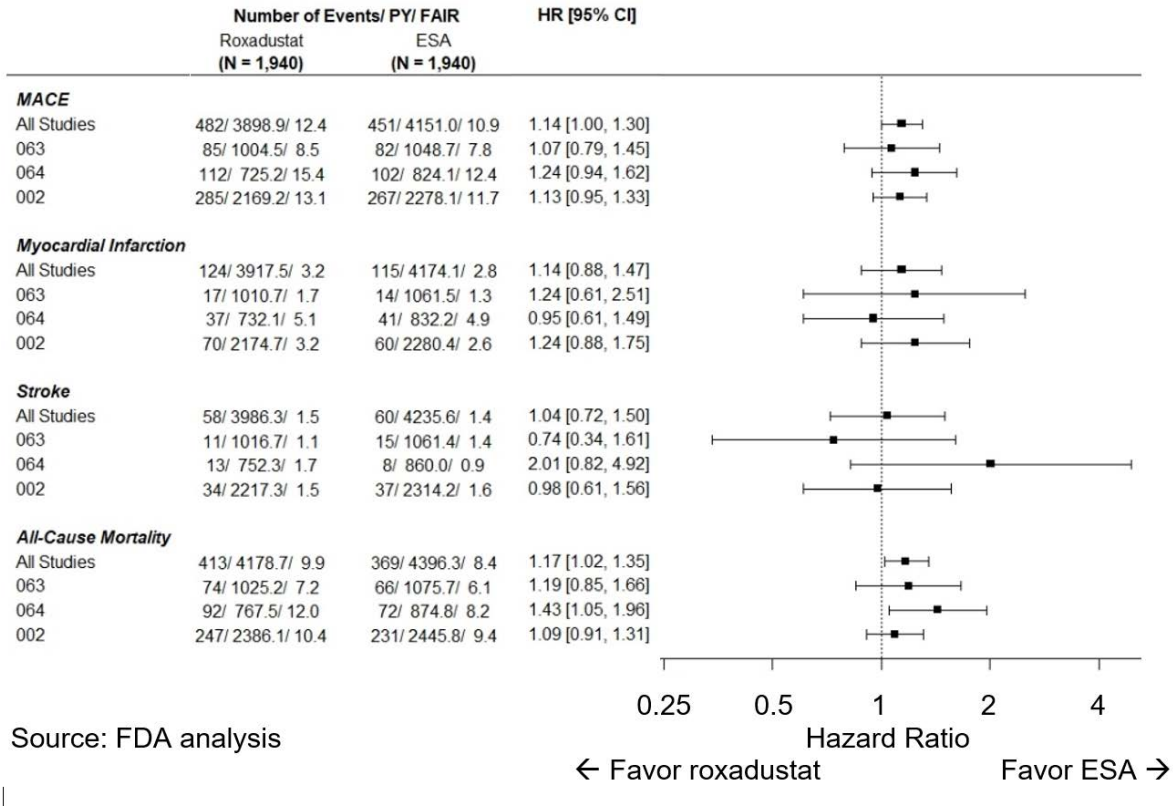
[3] Note that for this composite endpoint, the sums of the individual component events do not equal the total numbers of first MACE.

Figure 11: MACE and its Components for Studies in the DD Population (OT+7 Analysis)



Source: FDA Analysis

Figure 12: MACE and its Components for Studies in the DD Population (On-Study Analysis)



Source: FDA analysis

Adjudicated Death: During the OT+7 period in the combined DD studies, there were 207 and 232 deaths in roxadustat and epoetin alfa treated subjects, respectively, with exposure-adjusted rates of 6.2 and 6.1 per 100 P-Y. The estimated HR was 1.02 (0.84, 1.23) (Figure 11).

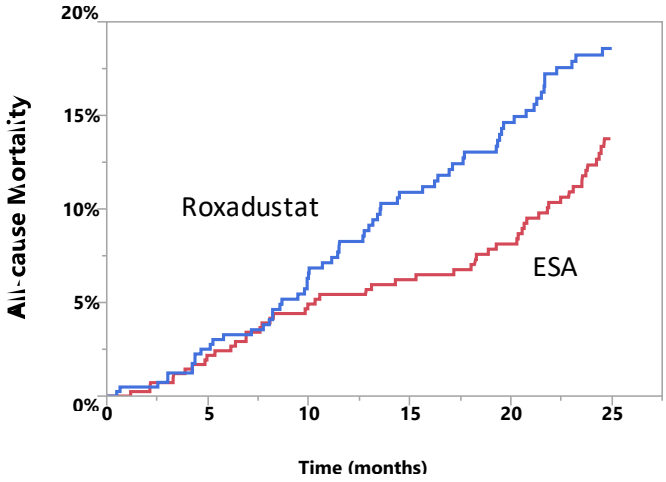
In the On-Study analysis, the HR was 1.17, with a 95% CI that excluded 1 (1.02, 1.35) (Figure 12). There were 413 and 369 deaths in roxadustat and epoetin alfa treated subjects, respectively, with exposure-adjusted rates of 9.9 and 8.4 per 100 P-Y. The estimated HRs for all-cause mortality were fairly consistent across the 4 studies, and ranging from 1.09 to 1.43.

Study 613

Study 613 was not part of the pooled analysis because of differences in study design, however, there were 57 deaths (8.9 per 100 PY) in roxadustat-treated patients (N = 414) vs. 45 (6.3 per 100 PY) in the ESA group (N = 420) in the OT+7 ascertainment window. The nominal HR was 1.54, and the 95% CI (1.04, 2.28) excluded 1. There were additional deaths in the OT+28 and On-study analyses; however, the estimated HRs were similar and the 95% CIs also excluded 1.

Figure 13 shows the Kaplan-Meier graph for all-cause mortality for Study 613, OT+28 ascertainment window.

Figure 13: All-cause Mortality—Study 613; OT+28 Ascertainment Window



Relation Between Thrombotic Events, Roxadustat Dose, Hb Level, and Hb Rate of Change

The relation between the risk of adverse cardiovascular events, ESA dose, Hb concentration, and Hb rate of change has been of longstanding interest to FDA. The issues were initially raised in FDA's 2001 review of the Biologics License Application for darbepoetin alfa [10]. Given the similar nature of the safety signals for darbepoetin alfa and roxadustat and questions about roxadustat dose and excursions in Hb, we performed similar analyses for thromboembolic adverse events for the key studies in the roxadustat application, and asked the applicant to conduct the analyses to corroborate our findings.

Analyses were conducted for the OT+7 ascertainment window, separately for the NDD and DD populations. Only the first thromboembolic event was considered for patients who experienced more than one event.

Thromboembolic Events in Relation to Drug Dose

A. The mean study drug dose (adjusted for weight) was calculated for each subject, and subjects were arranged in quintiles on this basis (by treatment group). The numbers of thromboembolic events were tabulated by dose quintile for both treatment groups and expressed as percent of subjects with events.

B. Because these drugs are titrated to effect throughout the treatment period, an alternative analysis was conducted using a moving average of the dose. Specifically, for each week on treatment, the mean weight-adjusted dose was calculated for the preceding 4 weeks. For example, the dose at Week 16 was the mean dose during Weeks 12 through 16. Based on the mean weight-adjusted dose for each week, the patient-weeks were divided into quintiles, and the numbers of thromboembolic events were tabulated by quintile for both treatment groups. Event rates were expressed as events per 52 patient-weeks (P-Y). A similar analysis was conducted on the basis of the weight-adjusted dose during 2-week intervals preceding the events. Finally, the analysis was conducted on the basis of the weight-adjusted dose most proximal to the event (previous week).

NDD Patient Population

The relation between overall weight-adjusted study agent dose and thromboembolic events is shown in Figure 14 for the NDD subject population. The figure shows the 5 quintiles from lowest (Q1) to highest (Q5) dose. The y-axis shows the percent of subjects with events, and the numbers in each bar represent the numbers of subjects with events. There appear to be fewer events in Q1, the quintile with the lowest overall weight-adjusted dose.

Figure 14: Thromboembolic Events vs. Overall Total Weight-adjusted Dose of Study Agent—NDD Population

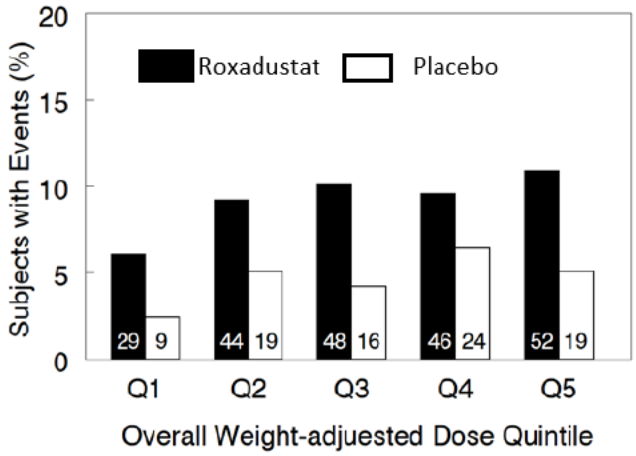
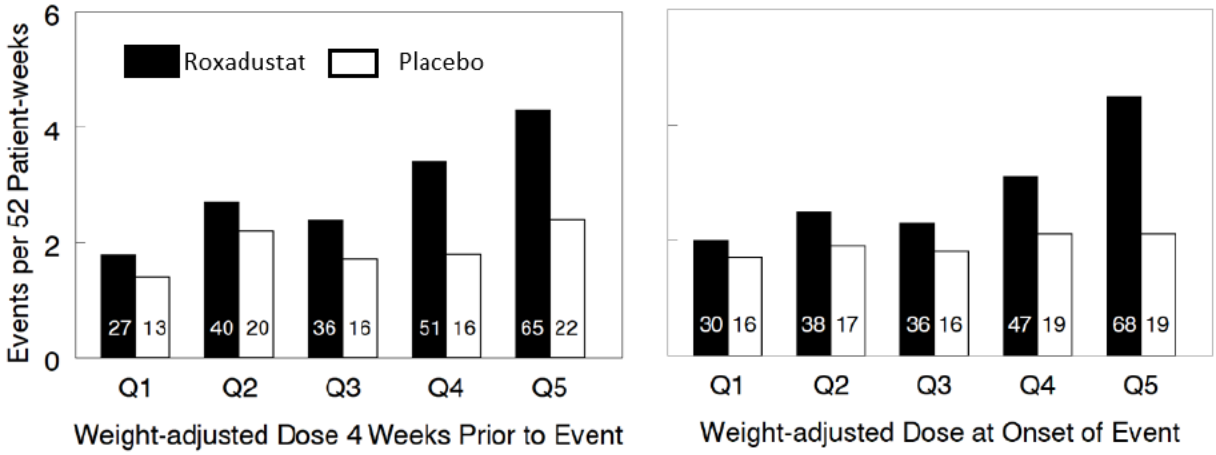


Figure 15 shows the relation between the rate of thromboembolic events (per 52 patient-weeks) and the weight-adjusted doses administered in the 4 weeks preceding the event (left) and the week preceding the event (right). The numbers inside the bars represent the numbers of events. Here, there are fairly strong associations between the preceding dose and thromboembolic events in roxadustat-

treated subjects. As expected, no association is evident in subjects who received placebo. The results for the 2 analyses are similar.

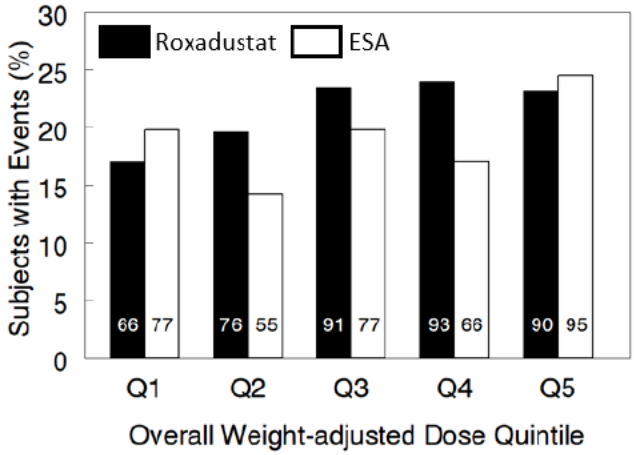
Figure 15: Thromboembolic Events vs. Weight-adjusted Dose of Study Agent—Received in Preceding 4 Weeks (Left); Received at Onset of Event (Right)—NDD Population



DD Patient Population

Figure 16 shows relations between weight-adjusted study agent dose and thromboembolic events. There appears to be a weak association between total dose and probability of a thromboembolic event in roxadustat-treated subjects. For subjects who received ESAs, there is no clear association.

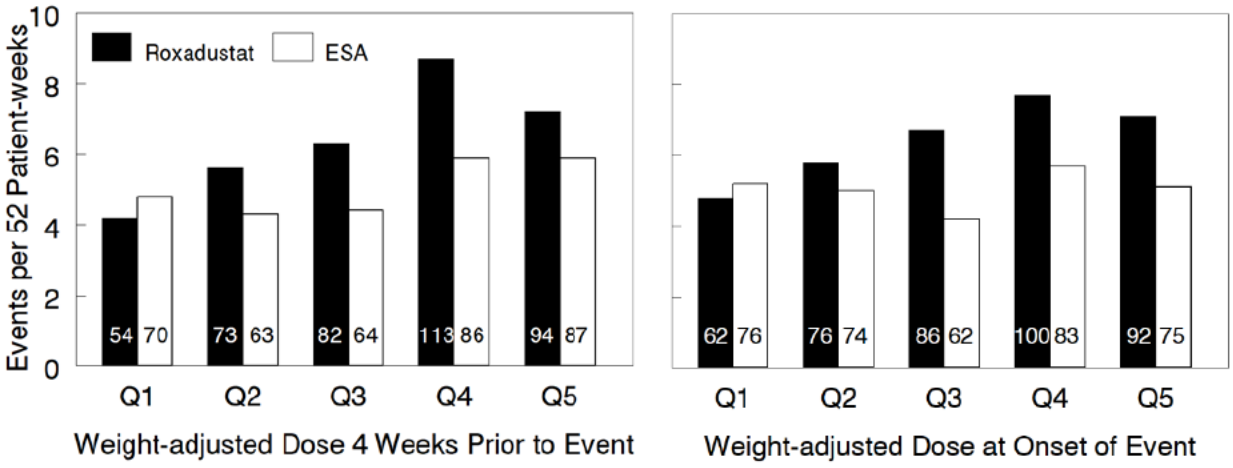
Figure 16: Thromboembolic Events vs. Overall Total Weight-adjusted Dose of Study Agent—DD Population



For subjects who received ESAs, the association is not clear. The results for the two analyses are similar.

Figure 17 shows a reasonable association between weight-adjusted dose and the rate of thromboembolic events in subjects who received roxadustat. For subjects who received ESAs, the association is not clear. The results for the two analyses are similar.

Figure 17: Thromboembolic Events vs. Weight-adjusted Dose of Study Agent—Received in Preceding 4 weeks (Left); Received at Onset of Event (Right)—DD Population



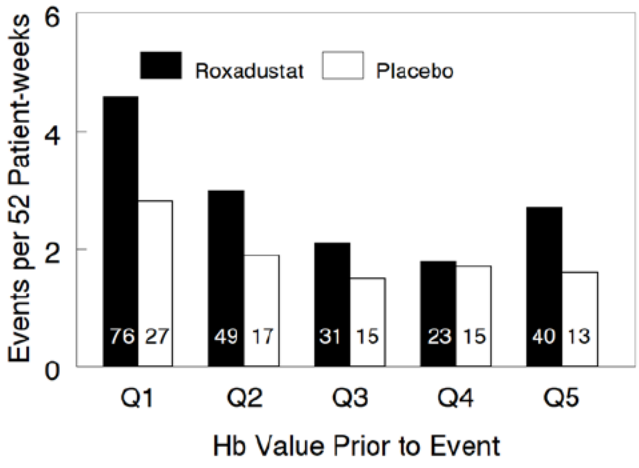
Thromboembolic Events in Relation to Hb Concentration

Hb values were estimated for all subjects for all weeks on-treatment, and the patient-weeks were placed into quintiles on this basis, separately by treatment arm. The numbers of thromboembolic events were assessed for each quintile for both treatment arms and expressed as rate per 52 patient-weeks.

NDD Patient Population

Figure 18 shows the relation between the rate of thromboembolic events and Hb concentration. It has been observed in a number of Hb target studies that subjects with lower Hb values are at higher risk of cardiovascular events. Thus, the relation seen in the figure is not surprising, although the increase in events in the highest quintile (Q5) in roxadustat-treated subjects suggests that targeting higher Hb values may lead to excess thromboembolic events.

Figure 18: Thromboembolic Events vs. Hb at the Time of Event—NDD Population

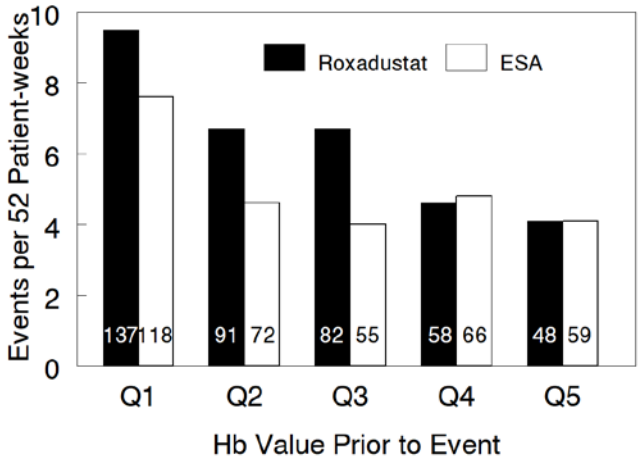


DD Patient Population

Figure 19 shows the relation between the rate of thromboembolic events and Hb concentration in the DD population, and once again there are greater numbers of cardiovascular events with lower Hb

values. The greater event rate in Q5 in the roxadustat subjects is not observed here as is was in the NDD population.

Figure 19: Thromboembolic Events vs. Hb at the Time of Event—DD Population



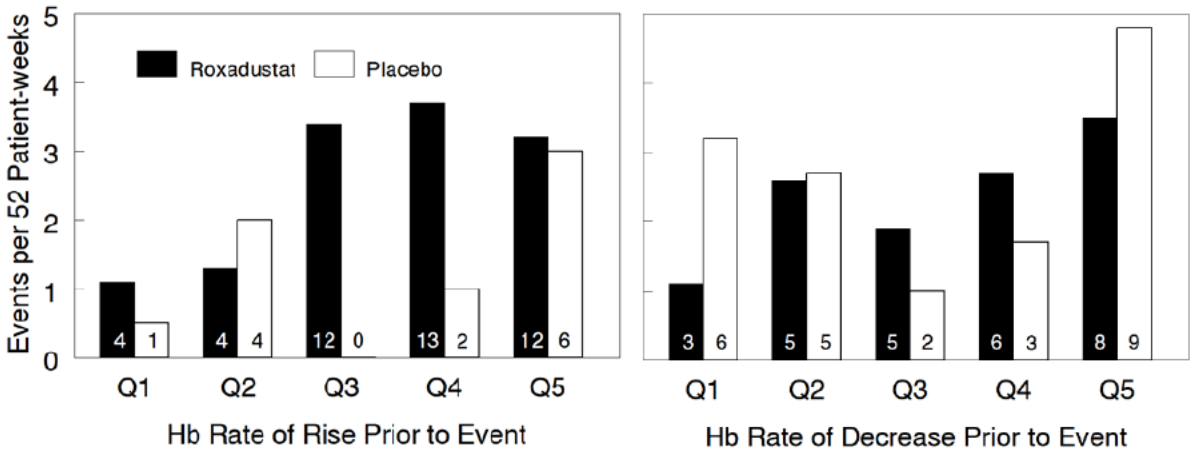
Thromboembolic Events in Relation to Hb Rate of Change

The Hb rate of change (g/dL/week) was estimated for each week that each subject was on treatment by fitting a linear regression line through the Hb values obtained during the preceding 4 weeks. Patient-weeks with a rising Hb level (Hb vs. time slope was ≥ 0) were placed in quintiles. The adverse events were tabulated for each quintile for both treatment arms, and results were expressed as adverse events per 52 patient-weeks (P-Y). A similar analysis was conducted for Hb rate of decline, based on patient-weeks with a falling Hb level (Hb vs. time slope < 0). Of note, rates of rise and decline could be estimated for only a limited number of events because Hb assessments were scheduled less frequently later in the trials, and two values were necessary to calculate a slope. The majority of the thromboembolic events occurred when only one Hb assessment was available and rate of change could not be estimated.

NDD Patient Population

Figure 20 shows the relation between thromboembolic events an Hb rate of rise leading up to the event. The numbers of events are quite small; most events did not have two Hb values leading up to the event that were necessary to calculate a slope. Nevertheless, there appears to be an association suggesting that limiting Hb rate of rise could decrease the incidence of thromboembolic events.

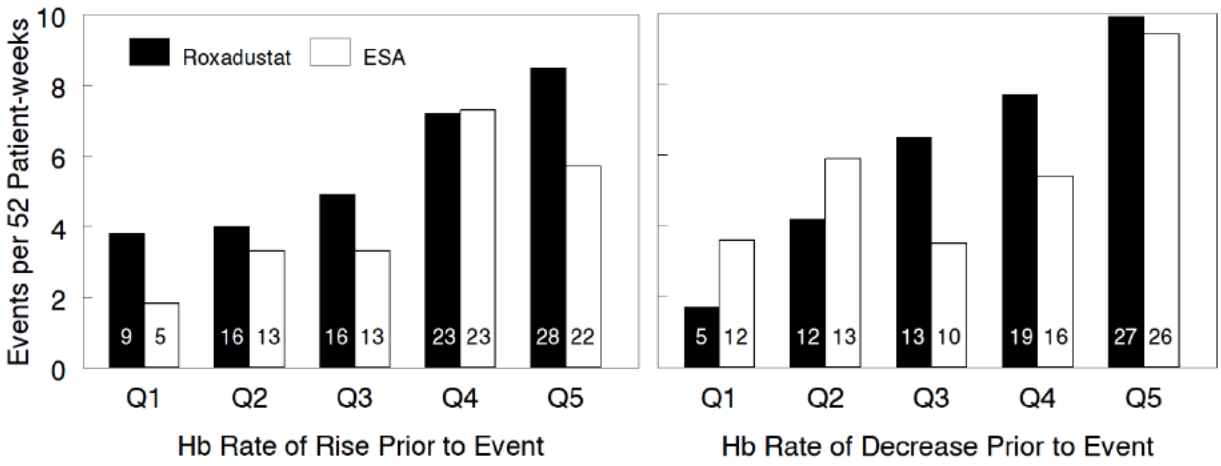
Figure 20: Thromboembolic Events vs. Hb Rate of Change Leading to Event—NDD Population



DD Patient Population

For the DD population, there were greater numbers of thromboembolic events for which a Hb slope could be calculated (Figure 21). There is a notable association between thromboembolic events and slope for both treatment groups, suggesting that measures to limit Hb rate of rise could decrease the frequency of thromboembolic events.

Figure 21: Thromboembolic Events vs. Hb Rate of Change Leading to Event—DD Population



Summary of Important Risks

Death

The results for all-cause mortality are difficult to interpret. In both the NDD and DD patient populations, the results of the meta-analyses are nearly neutral for the primary analyses, but nominally statistically significantly unfavorable for roxadustat in the sensitivity analyses. Specifically, for the NDD patient population, the estimated HR for the primary on-study analysis is 1.08, whereas there is a nominally statistically significant finding (not favoring roxadustat) for the OT+7 sensitivity analysis (HR = 1.40; 95% CI 1.08, 1.82). For the DD population, the estimated HR for the primary OT+7 analysis was 1.02, whereas the HR for the on-study sensitivity analysis was nominally statistically significant (HR 1.17, 95% CI 1.02,

1.35). Although Study 613 was not one of the studies in the meta-analysis, its mortality finding is a concern. In general, concordance between primary statistical analyses and sensitivity analyses provides confidence in the validity of the results. With the observed discordance here, the results are inconclusive.

Other important risks of MI, stroke, thrombosis, device/shunt thrombosis, systemic hypertension, seizure, and malignancy are summarized separately for the NDD and DD populations.

NDD Population

Table 30 summarizes the more important risks in the NDD patient population, as extracted from the principal data sources in the NDA. Note that the sample sizes and methods of expression differ among the sources. For studies 001, 060, and 068, the numbers in parentheses in the "Roxadustat" and "Comparator" columns represent rates per 100 P-Y. For study 610, the numbers in parentheses represent percent of subjects. Risk differences and relative risk are based on events per 100 P-Y for Studies 001, 060, 068, and percent of subjects for Study 610. For relative risk, the vertical dashed line is set to 1.0.

Table 30: Important Risks in the NDD Patient Population; Combined Data Sources

	Roxadustat	Comparator	Risk Difference	Relative Risk
Myocardial Infarction				
Studies 001, 060, 068; MACE - On-study	86 (1.9)	52 (1.5)	0.4	1.3
Studies 001, 060, 068; MACE - OT+7	72 (1.9)	37 (1.6)	0.3	1.2
Studies 001, 060, 068; Serious AEs	54 (1.4)	31 (1.3)	0.1	1.1
Study 610	7 (2.2%)	8 (2.7%)	-0.5	0.8
Stroke				
Studies 001, 060, 068; MACE - On-study	56 (1.2)	36 (1.1)	0.1	1.3
Studies 001, 060, 068; MACE - OT+7	48 (1.2)	21 (0.9)	0.3	1.5
Studies 001, 060, 068; Serious AEs	53 (1.3)	26 (1.1)	0.3	1.2
Study 610	2 (0.6%)	5 (1.7%)	-1.1	0.4
Thrombosis				
Studies 001, 060, 068; Serious AEs	140 (3.6)	58 (2.5)	1.10	1.5
Studies 001, 060, 068; All AEs	195 (4.1)	76 (2.0)	2.10	2.0
Study 610; Serious AEs	20 (6.2%)	13 (4.4%)	1.80	1.4
Study 610; All AEs	25 (7.7%)	15 (5.1%)	2.60	1.5
Device/Shunt Thrombosis				
Studies 001, 060, 068; Serious AEs	36 (0.9)	8 (0.3)	0.60	2.7
Studies 001, 060, 068; All AEs	88 (1.8)	20 (0.5)	1.30	3.4
Systemic Hypertension				
Studies 001, 060, 068; Serious AEs	75 (1.9)	46 (2.0)	0.40	1.3
Studies 001, 060, 068; All AEs	411 (8.6)	224 (6.0)	2.60	1.4
Study 610; Serious AEs	9 (3%)	8 (3%)	0.00	1.0
Study 610; All AEs	87 (27%)	90 (31%)	-4.0	0.9
Seizures				
Studies 001, 060, 068; Serious AEs	9 (0.2)	1 (0)	0.20	5.4
Studies 001, 060, 068; All AEs	24 (0.5)	3 (0.1)	0.40	6.2
Study 610; Serious AEs	2 (0.6%)	0 (0%)	0.60	-
Malignancy				
Studies 001, 060, 068; Serious AEs	37 (1.0)	23 (1.0)	0.00	1.0
Studies 001, 060, 068; All AEs	43 (0.9)	34 (0.9)	0.00	1.0
Study 610; Serious AEs	9 (3%)	7 (2%)	0.40	1.2

Relative to placebo, there are signals for all of the thrombotic adverse events, particularly the thrombosis query (RR ≅ 1.6) and device/shunt thrombosis (RR ≅ 3). Seizures have a RR ≅ 6. Malignancy is neutral. Myocardial infarction, stroke, and hypertension have RRs in the 1.2- to 1.3-range, which are difficult to interpret given the differential rates of dropout between subjects who received roxadustat and placebo.

Adverse Events by Subgroup

Table 31 shows adverse events in the OT+7 ascertainment window for four major risks by subgroup. The numbers in the table represent events per 100 P-Y. Relative risks (RR) are unitless. Continuous variables are shown in quartiles, e.g., age, body mass index (BMI), baseline Hb, and baseline GFR.

Table 31: Major Risks by Subgroup in the NDD Population (All Adverse Events; OT+7 Analysis)

Events per 100 P-Y		Percent of Subjects	Thrombosis, all			Device/shunt thrombosis, occlusion, malfunction, stenosis			Sepsis			Seizure		
			Rox	Pbo	RR	Rox	Pbo	RR	Rox	Pbo	RR	Rox	Pbo	RR
All	All	100%	5.0	3.3	1.5	2.3	0.9	2.6	2.6	1.2	2.1	0.6	0.1	4.8
Sex	Female	58%	4.8	2.7	1.8	2.5	0.8	3.2	2.4	0.8	3.0	0.7	0.1	4.7
	Male	42%	5.5	4.2	1.3	1.9	1.0	2.0	2.8	1.8	1.6	0.5	0.1	4.9
Baseline age quartile	18-53	24%	3.7	1.8	2.1	3.4	1.4	2.4	2.0	0.8	2.5	1.0	0.4	2.4
	54-63	26%	5.9	4.3	1.4	2.4	0.9	2.9	2.4	1.2	2.0	0.6	0.0	-
	64-72	24%	5.3	3.5	1.5	2.0	0.5	3.9	3.5	1.0	3.5	0.5	0.0	-
	73-100	25%	5.2	3.3	1.6	1.3	0.8	1.6	2.4	1.7	1.4	0.4	0.2	2.7
Age ≥ 65	No	53%	4.9	3.3	1.5	2.9	1.1	2.5	2.2	1.0	2.3	0.7	0.2	4.1
	Yes	47%	5.3	3.3	1.6	1.6	0.6	2.6	3.1	1.5	2.1	0.5	0.1	5.9
Age ≥ 75	No	79%	5.1	3.1	1.7	2.5	0.9	2.8	2.5	1.1	2.4	0.6	0.1	5.8
	Yes	21%	4.7	3.9	1.2	1.4	0.7	1.9	2.7	1.7	1.6	0.5	0.2	2.8
Baseline BMI quartile	15-22.78	25%	2.9	1.9	1.5	2.3	0.7	3.3	2.2	0.9	2.5	0.6	0.5	1.1
	22.79-25.82	25%	5.2	4.4	1.2	2.0	0.8	2.4	3.2	1.0	3.1	0.4	0.0	-
	25.83-29.76	25%	5.6	3.7	1.5	2.5	1.2	2.0	2.8	1.4	2.0	0.7	0.0	-
	29.77-60.3	25%	6.6	3.0	2.2	2.4	0.7	3.5	2.1	1.5	1.4	0.7	0.0	-
Race	Asian	36%	3.5	2.6	1.3	1.7	0.4	4.7	3.0	1.6	1.9	0.6	0.1	4.9
	Black	8%	4.9	4.3	1.1	1.2	1.4	0.9	1.8	0.9	1.9	1.2	0.0	-
	Other	8%	5.2	1.5	3.4	1.0	0	-	2.6	0.5	5.2	0.7	0.0	-
	White	47%	6.4	3.9	1.7	3.2	1.3	2.5	2.3	1.1	2.1	0.5	0.2	2.8
Baseline hemoglobin quartile	4.9-8.72	25%	5.8	4.3	1.3	3.0	0.9	3.5	4.0	1.9	2.1	0.8	0.2	3.7
	8.73-9.23	25%	4.6	3.7	1.3	2.1	1.3	1.6	3.0	0.9	3.3	0.8	0.0	-
	9.24-9.63	25%	5.2	2.7	1.9	2.1	0.3	6.6	2.3	1.3	1.8	0.3	0.3	1.0
	9.64-10.57	25%	4.7	2.8	1.7	2.0	1.0	2.0	1.2	0.9	1.3	0.6	0.0	-
History of CV disease	No	68%	4.4	2.5	1.8	2.3	0.8	3.0	2.3	1.1	2.2	0.6	0.1	4.4
	Yes	32%	6.4	4.9	1.3	2.3	1.1	2.2	3.1	1.5	2.2	0.8	0.1	5.8
Baseline eGFR quartile	1.6-11.07	25%	7.9	5.6	1.4	6.2	2.2	2.8	3.6	1.8	2.0	0.7	0.4	1.5
	11.1-16.97	25%	6.5	3.5	1.9	2.5	1.1	2.3	2.6	1.1	2.4	0.5	0.0	-
	17.0-25.99	25%	3.0	3.3	0.9	0.5	0.7	0.8	1.6	1.0	1.6	0.7	0.2	4.3
	26.0-75.2	25%	3.2	1.7	1.9	0.4	0	-	2.7	1.1	2.4	0.6	0.0	-
History of diabetes	No	43%	4.9	3.1	1.6	3.2	1.5	2.1	1.8	1.0	1.8	0.6	0.3	1.9
	Yes	57%	5.1	3.4	1.5	1.5	0.4	4.0	3.2	1.3	2.4	0.7	0.0	-

Rox = roxadustat; Pbo = placebo; RR = relative risk; BMI = body mass index; eGFR = estimated glomerular filtration rate

For thrombosis (yellow column), the RRs are fairly consistent across subgroups; however, there are subgroups where risk trends higher. For example, a higher risk of thrombosis is evident in subjects with higher BMI, lower baseline Hb, and lower eGFR. The risk of sepsis (blue column) tends to be higher in

older subjects, as well as subjects with lower baseline Hb, lower baseline eGFR, and a history of CV disease or diabetes. Seizure risk (purple column) is higher in younger subjects. It is important to recognize that these are relatively small numbers of events; therefore, these estimates are subject to considerable uncertainty.

DD Population

Table 32 shows the important risks in the DD patient population. Note that the sample sizes and methods of expression differ among the sources. For studies 002, 063, and 064, the numbers in parentheses in the "Roxadustat" and "ESA" columns represent rates per 100 P-Y. For study 613, the numbers in parentheses represent percent of subjects. Risk differences and relative risk are based on events per 100 P-Y for Studies 002, 063, 064, and percent of subjects for Study 613. For relative risk, the vertical dashed line is set to 1.0. Note there are far more adverse events here than in the NDD subject population.

Table 32: Important Risks in the DD Patient Population

	Roxadustat	ESA	Risk Difference	Relative Risk
Myocardial Infarction				
Studies 002, 063, 064; MACE - OT+7	103 (3.1)	109 (3.0)	0.1	1.07
Studies 002, 063, 064; MACE - On-study	124 (3.2)	115 (2.8)	0.4	1.14
Studies 002, 063, 064; Serious AEs	88 (2.7)	85 (2.3)	0.4	1.2
Study 613	10 (2.4%)	17 (4.0%)	-1.6	0.6
Stroke				
Studies 002, 063, 064; MACE - OT+7	45 (1.4)	50 (1.3)	0.1	1.0
Studies 002, 063, 064; MACE - On-study	58 (1.5)	60 (1.4)	0.1	1.0
Studies 002, 063, 064; Serious AEs	51 (1.5)	49 (1.3)	0.2	1.2
Study 613	4 (1%)	8 (2%)	-0.9	0.5
Thrombosis				
Studies 002, 063, 064; Serious AEs	241 (7.3)	201 (5.4)	1.9	1.4
Studies 002, 063, 064; All AEs	392 (11.8)	344 (9.2)	2.6	1.3
Study 613; Serious AEs	52 (13%)	43 (10%)	2.4	1.2
Study 613; All AEs	77 (19%)	65 (16%)	3.1	1.2
Device/Shunt Thrombosis				
Studies 002, 063, 064; Serious AEs	121 (3.7)	94 (2.5)	1.1	1.5
Study 613; Serious AEs	35 (9%)	22 (5%)	3.3	1.6
Systemic Hypertension				
Studies 002, 063, 064; Serious AEs	89 (2.7)	110 (2.9)	-0.30	0.9
Studies 002, 063, 064; All AEs	365 (11.0)	367 (9.8)	1.20	1.1
Study 613; Serious AEs	13 (3%)	8 (2%)	1.20	1.2
Study 613; All AEs	79 (19%)	85 (20%)	-1.1	0.9
Seizures				
Studies 002, 063, 064; Serious AEs	26 (0.8)	19 (0.51)	0.27	1.6
Studies 002, 063, 064; All AEs	45 (1.4)	33 (0.9)	0.50	1.5
Study 613; Serious AEs	2 (0.5%)	4 (1%)	-0.50	0.5
Malignancy				
Studies 002, 063, 064; Serious AEs	23 (0.7)	28 (0.8)	-0.10	0.9
Studies 002, 063, 064; All AEs	42 (1.3)	48 (1.3)	0.00	1.0
Study 613; Serious AEs	15 (4%)	15 (4%)	0.00	1.0

Relative to epoetin alfa, there are signals for MI (RR ≅ 1.1), thrombosis (RR ≅ 1.3), device/shunt thrombosis (≅ 1.5), and seizures (RR ≅ 1.5). Stroke, hypertension, and malignancy are neutral (again, however, relative to epoetin alfa, for which these are labeled adverse drug reactions).

Adverse Events by Subgroup

Table 33 shows adverse events in the OT+7 ascertainment window for four major risks by subgroup. The numbers in the table represent events per 100 P-Y. Relative risks (RR) are unitless. Continuous variables are shown in quartiles, e.g., age, body mass index (BMI), baseline Hb, and baseline GFR

Table 33: Major Risks by Subgroup in the DD Population (All Adverse Events; OT+7 Analysis)

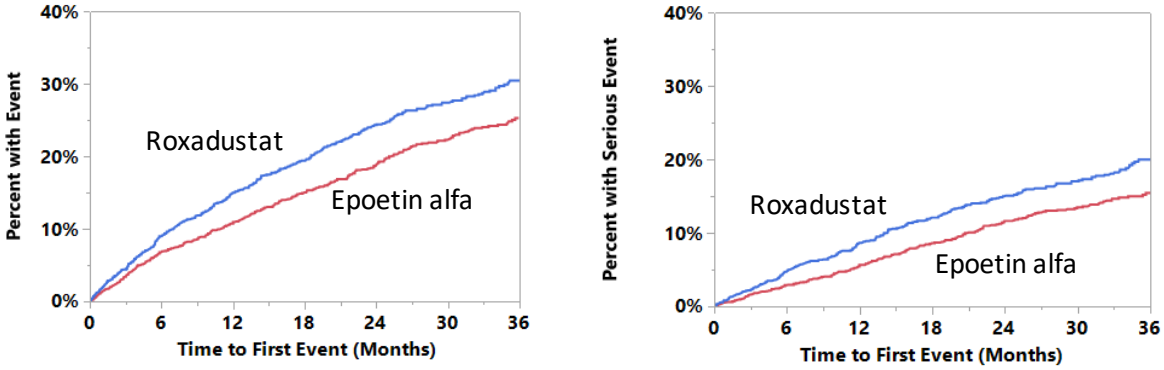
Events per 100 P-Y		Percent of Subjects	Thrombosis, all			Device/shunt thrombosis, occlusion, malfunction, stenosis			Sepsis			Seizure		
			Rox	EPO	RR	Rox	EPO	RR	Rox	EPO	RR	Rox	EPO	RR
All	All	100%	9.4	7.8	1.2	7.6	6.3	1.2	3.2	3.0	1.1	1.1	0.8	1.4
Sex	Female	58%	10.0	8.1	1.2	8.7	7.0	1.2	3.0	3.0	1.0	0.8	0.6	1.4
	Male	42%	8.9	7.7	1.2	6.9	5.8	1.2	3.3	3.0	1.1	1.2	0.9	1.5
Baseline age quartile	18-44	25%	5.6	5.5	1.0	6.0	5.5	1.1	1.9	1.7	1.1	1.6	1.1	1.5
	45-56	26%	9.6	6.8	1.4	8.0	5.5	1.5	3.5	3.1	1.1	1.1	0.5	2.1
	57-65	25%	8.9	8.7	1.0	8.0	6.9	1.2	3.4	3.3	1.0	0.8	0.9	1.0
	66-94	24%	14.3	10 3	1.4	8.9	7.2	1.2	4.0	3.9	1.0	0.8	0.6	1.3
Age ≥ 65	No	73%	7.8	7.0	1.1	7.2	5.9	1.2	2.9	2.7	1.1	1.2	0.8	1.4
	Yes	27%	14.2	10 3	1.4	9.0	7.4	1.2	4.0	3.9	1.0	0.8	0.5	1.5
Age ≥ 75	No	91%	9.0	7.4	1.2	7.5	6.0	1.2	3.0	2.8	1.1	1.1	0.8	1.5
	Yes	9%	14.0	12 3	1.1	8.8	8.8	1.0	4.9	4.8	1.0	0.3	0.5	0.6
Baseline BMI quartile	14.6-22.83	25%	8.2	5.2	1.6	6.2	4.5	1.4	2.6	2.2	1.2	1.2	0.6	2.0
	22.83-26.37	25%	8.5	7.7	1.1	7.4	5.7	1.3	2.8	2.5	1.1	1.1	0.9	1.2
	26.37-30 9	25%	8.5	7.8	1.1	6.8	7.0	1.0	2.8	3.1	0.9	1.2	0.7	1.8
	31-64.9	25%	12.1	10.4	1.2	9.8	7.7	1.3	4.5	4.1	1.1	0.8	0.8	1.0
Race	Asian	14%	7.5	5.1	1.5	5.0	4.3	1.2	3.4	4.3	0.8	1.7	0.8	2.2
	Black	18%	13.0	9.4	1.4	11.9	8.6	1.4	4.0	2.7	1.5	1.3	0.8	1.6
	Other	7%	6.1	5.6	1.1	5.6	4	-	4.3	3.2	1.3	2.2	1.9	1.2
	White	61%	9.0	8.1	1.1	7.0	6.1	1.2	2.8	2.9	1.0	0.8	0.7	1.2
Baseline hemoglobin quartile	4.3-8.8	25%	8.2	7.0	1.2	7.3	5.7	1.3	2.3	1.7	1.4	1.6	0.5	3.2
	8.8-9.8	25%	10.0	8.2	1.2	8.9	6.5	1.4	3.1	2.5	1.2	1.0	0.8	1.3
	9.8-10.66	25%	10.5	9.6	1.1	7.3	7.8	0.9	3.5	4.7	0.7	1.0	1.0	1.0
	10.67-12 2	25%	8.8	6.5	1.3	7.2	5.1	1.4	3.5	2.9	1.2	0.8	0.7	1.1
History of CV disease	No	57%	7.4	5.5	1.3	6.5	4.7	1.4	2.2	2.3	0.9	1.1	0.7	1.6
	Yes	43%	12.2	11.0	1.1	9.2	8.4	1.1	4.6	4.0	1.1	1.0	0.8	1.2
Type of Dialysis	HD	90%	9.9	8.2	1.2	8.3	6.7	1.2	3.3	3.0	1.1	1.0	0.7	1.5
	PD	10%	4.4	4.2	1.1	1.6	2.1	0.7	1.6	3.1	0.5	1.6	1.3	1.2
History of diabetes	No	53%	7.0	6.4	1.1	6.5	5.5	1.2	1.9	2.0	0.9	1.0	0.5	1.8
	Yes	47%	12.4	9.6	1.3	9.1	7.2	1.3	4.7	4.2	1.1	1.2	1.0	1.2

Rox = roxadustat; EPO = epoetin alfa; RR = relative risk; HD = hemodialysis; PD = peritoneal dialysis

For thrombosis (yellow column), the RRs are fairly consistent across subgroups; however, there are subgroups where risk trends higher. For example, a higher risk of thrombosis is evident in older subjects, subjects with higher BMI, subjects with a history of cardiovascular disease, subjects on hemodialysis, subjects with diabetes, and possibly females. The risk of device/shunt thrombosis (orange column) follows the same pattern. Note that for subjects on hemodialysis, the rates of device/shunt thrombosis, occlusion, malfunction, stenosis are 8.3 and 6.7 per 100 P-Y for roxadustat and epoetin alfa, respectively, for a risk difference of 1.6 events per 100 P-Y. The risk of sepsis (blue column) increases with age, BMI, a history of cardiovascular disease, diabetes, and hemodialysis (the latter for roxadustat only). Seizure risk (purple column) is higher in younger subjects and possibly subjects with low baseline Hb. It is important to recognize that these are relatively small numbers of events; therefore, these estimates are subject to considerable uncertainty.

Given the importance of thromboembolic events, we performed a Kaplan-Meier time-to-first thrombotic event analysis for the DD subject population (Figure 22) for all (left) and serious (right) events. The OT+7 ascertainment window was used for the analyses.

Figure 22: Time to First Thrombotic Event—All Events (Left); Serious Events (Right) for the DD Population (Studies 002, 063, and 064); OT+7 Ascertainment Window



Source: FDA analysis

The excess risk accrues continuously throughout the three studies.

References

1. Hsu, C, 2002, Epidemiology of Anemia Associated with Chronic Renal Insufficiency, Curr Opin Nephrol Hypertens, 11(3):337-341.
2. Hsu, C, C McCulloch, and G Curhan, 2002, Epidemiology of Anemia Associated with Chronic Renal Insufficiency among Adults in the United States: Results from the Third National Health and Nutrition Examination Survey, J Am Soc Nephrol, 13(2):504–510..
3. United States Renal Data System (USRDS) 2020 Annual Report (https://adr.usrds.org/2020) [accessed 6/16/2021]
4. Besarab, A, W Bolton, J Browne, J Egrie, A Nissenson, D Okamoto, S Schwab, and D Goodkin, 1998, The Effects of Normal as Compared with Low Hematocrit Values in Patients with Cardiac Disease Who Are Receiving Hemodialysis and Epoetin, N Engl J Med, 339(9):584-590.
5. Singh, A, L Szczech, K Tang, H Barnhart, S Sapp, M Wolfson, D Reddan, and CHOIR Investigators, 2006, Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease, N Engl J Med, 355(20):2085-2098.
6. Drueke, T, F Locatelli, N Clyne, K Eckardt, I Macdougall, D Tsakiris, H Burger, A Scherhag, and CREATE Investigators, 2006, Normalization of Hemoglobin Level in Patients with Chronic Kidney Disease and Anemia, N Engl J Med, 355(20):2071–2084.
7. Lewis, E, M Pfeffer, A Feng, H Uno, J McMurray, R Toto, S Gandra, S Solomon, M Moustafa, I Macdougall, F Locatelli, P Parfrey, and TREAT Investigators, 2011, Darbepoetin Alfa Impact on Health Status in Diabetes Patients with Kidney Disease: A Randomized Trial, Clin J Am Soc Nephrol, 6(4):845–855.
8. MacMurray, J. et al., Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. Kidney Int Suppl 2012; 2(4):279–335.
9. Unger, E, A Thompson, M Blank, R Temple, 2010, Erythropoiesis-Stimulating Agents—Time for a Reevaluation, N Engl J Med, 362(3):189–192.
10. Unger, E.F., "Clinical Review of Darbepoetin alfa;" Food and Drug Administration (https://www.fda.gov); archived at Wayback Machine (https://web.archive.org/); https://web.archive.org/web/20161024172128/http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm086019.pdf [accessed 6/9/2021]

Appendix

Approved Epogen Label

https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/103234s5369lbl.pdf (accessed 6/21/2021)

Adverse Event Preferred Terms Used in Key Queries

Table 34: Terms in Key Adverse Event Queries

Thrombosis	Device/shunt thrombosis/ occlusion/malfunction/stenosis	Stroke
Cerebral infarction	Thrombosis in device	Cerebral infarction
Embolic cerebral infarction	Arteriovenous fistula thrombosis	Embolic cerebral infarction
Ischaemic stroke	Arteriovenous graft thrombosis	Ischaemic stroke
Cerebellar infarction	Vascular access site thrombosis	Cerebellar infarction
Lacunar stroke	Vascular graft thrombosis	Lacunar stroke
Embolic stroke	Medical device site thrombosis	Embolic stroke
Brain stem stroke	Device occlusion	Brain stem stroke
Lacunar infarction	Arteriovenous fistula occlusion	Lacunar infarction
Thrombosis in device	Vascular access site occlusion	Cerebrovascular accident
Arteriovenous fistula thrombosis	Vascular access complication	Haemorrhagic stroke
Arteriovenous graft thrombosis	Vascular access malfunction	Brain stem haemorrhage
Vascular access site thrombosis	Arteriovenous graft site stenosis	
Vascular graft thrombosis	Shunt occlusion	**Sepsis/septic shock**
Graft thrombosis	Shunt malfunction	
Shunt thrombosis	Vascular graft stenosis	Device related sepsis
Acute myocardial infarction	Anastomotic stenosis	Enterococcal sepsis
Myocardial infarction	Vascular access site complication	Sepsis
Deep vein thrombosis	Vascular graft occlusion	Urosepsis
Thrombosis		Streptococcal sepsis
Atrial thrombosis	**Device/shunt thrombosis**	Pseudomonal sepsis
Peripheral artery thrombosis		Staphylococcal sepsis
Subclavian vein thrombosis	Thrombosis in device	Septic shock
Brachiocephalic vein thrombosis	Arteriovenous fistula thrombosis	Sepsis syndrome
Subclavian artery thrombosis	Arteriovenous graft thrombosis	Biliary sepsis
Vena cava thrombosis	Vascular access site thrombosis	Bacterial sepsis
Thrombophlebitis superficial	Vascular graft thrombosis	Fungal sepsis
Arterial thrombosis	Graft thrombosis	Citrobacter sepsis
Thrombophlebitis	Shunt thrombosis	Listeria sepsis
Jugular vein thrombosis	Medical device site thrombosis	Abdominal sepsis
Venous thrombosis	Device related thrombosis	Septic encephalopathy
Pelvic venous thrombosis	Injection site thrombosis	Escherichia sepsis
Venous thrombosis limb		
Cardiac ventricular thrombosis	**Seizure FDA**	
Intracardiac thrombus		
	Epilepsy	
	Epileptic encephalopathy	
	Seizure	
	Generalised tonic-clonic seizure	
	Idiopathic partial epilepsy	
	Partial seizures	
	Tonic convulsion	