Treatments for Anemia in Chronic Kidney Disease: Effectiveness and Value

Final Evidence Report

March 5, 2021

Prepared for

April 19, 2022: New evidence regarding treatments and therapies gets published on an ongoing basis. ICER reached out to patient and clinical experts and the relevant manufacturers included in this review 12 months after the publication of this report, giving them an opportunity to submit public comments regarding new relevant evidence or information on coverage that they wish to highlight. No stakeholders submitted public comments. ICER has launched ICER Analytics to provide stakeholders an opportunity to work directly with ICER models and examine how changes in parameters would affect results. You can learn more about ICER Analytics here.

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Reem Mustafa served as the lead author for the report. Grace Fox led the systematic review and authorship of the comparative clinical effectiveness section in collaboration with Foluso Agboola and Noemi Fluetsch. Lisa Bloudek was responsible for the development of the cost-effectiveness model with support from Josh J. Carlson. Jonathan D. Campbell was responsible for the oversight of the cost-effectiveness analyses and developed the budget impact model. David M. Rind and Steven D. Pearson provided methodologic guidance on the clinical and economic evaluations. We would also like to thank Laura Cianciolo, Rick Chapman, and Azanta Thakur for their contributions to this report.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. Through all its work, ICER seeks to help create a future in which collaborative efforts to move evidence into action provide the foundation for a more effective, efficient, and just health care system. More information about ICER is available at https://icer.org/.

The funding for this report comes from government grants and non-profit foundations, with the largest single funder being Arnold Ventures. No funding for this work comes from health insurers, pharmacy benefit managers, or life science companies. ICER receives approximately 29% of its overall revenue from these health industry organizations to run a separate Policy Summit program, with funding approximately equally split between insurers/PBMs and life science companies. Life science companies relevant to this review who participate in this program include AstraZeneca and Pfizer. For a complete list of funders and for more information on ICER's support, please visit https://icer.org/who-we-are/independent-funding/

For drug topics, in addition to receiving recommendations from the public, ICER scans publicly available information and also benefits from a collaboration with IPD Analytics, an independent organization that performs analyses of the emerging drug pipeline for a diverse group of industry stakeholders, including payers, pharmaceutical manufacturers, providers, and wholesalers. IPD provides a tailored report on the drug pipeline on a courtesy basis to ICER but does not prioritize topics for specific ICER assessments.

About CTAF

The California Technology Assessment Forum (CTAF) – a core program of ICER – provides a public venue in which the evidence on the effectiveness and value of health care services can be discussed with the input of all stakeholders. CTAF seeks to help patients, clinicians, insurers, and policymakers interpret and use evidence to improve the quality and value of health care.

The CTAF Panel is an independent committee of medical evidence experts from across California, with a mix of practicing clinicians, methodologists, and leaders in patient engagement and advocacy. All Panel members meet strict conflict of interest guidelines and are convened to discuss the evidence summarized in ICER reports and vote on the comparative clinical effectiveness and value of medical interventions. More information about CTAF is available at https://icer.org/who-we-are/people/independent-appraisal-committees/ctaf/.

The findings contained within this report are current as of the date of publication. Readers should be aware that new evidence may emerge following the publication of this report that could potentially influence the results. ICER may revisit its analyses in a formal update to this report in the future.

The economic models used in ICER reports are intended to compare the clinical outcomes, expected costs, and cost effectiveness of different care pathways for broad groups of patients. Model results therefore represent average findings across patients and should not be presumed to represent the clinical or cost outcomes for any specific patient. In addition, data inputs to ICER models often come from clinical trials; patients in these trials and provider prescribing patterns may differ in real-world practice settings.

In the development of this report, ICER's researchers consulted with several clinical experts, patients, manufacturers, and other stakeholders. The following experts provided input that helped guide the ICER team as we shaped our scope and report. It is possible that expert reviewers may not have had the opportunity to review all portions of this draft report. None of these individuals is responsible for the final contents of this report, nor should it be assumed that they support any part of it. The report should be viewed as attributable solely to the ICER team and its affiliated researchers.

For a complete list of stakeholders from whom we requested input, please visit: http://icerorg.wpengine.com/wp-content/uploads/2020/10/ICER_Anemia_in_CKD_Stakeholder_List_072020.pdf.

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Supplemental Materials

List of Acronyms and Abbreviations Used in this Report

AHRQ	Agency for Healthcare Research and Quality
AMCP	Academy of Managed Care Pharmacy
CFB	Change from baseline
CI	Confidence interval
CKD	Chronic kidney disease
CRP	C-reactive protein
DD	Dialysis dependent
DI	Dialysis independent
eGFR	Estimated glomerular filtration rate
ESA	Erythropoiesis-stimulating agent
ESKD	End-stage kidney disease
ESRD	End-stage renal disease
evLYG	Equal value life years gained
FDA	Food and Drug Administration
g/dL	Grams per deciliter
GFR	Glomerular filtration rate
Hb	Hemoglobin
HD	Hemodialysis
HDL	High-density lipoprotein
HIF	Hypoxia-inducible factor
HIF-PH	Hypoxia-inducible factor prolyl hydroxylase
HR	Hazard ratio
HRQoL	Health-related quality of life
ID	Incident dialysis
IV	Intravenous
LDL	Low-density lipoprotein
LSM	Least squares mean
LY	Life year
MACE	Major adverse cardiovascular event
MCID	Minimum clinically important difference
MD	Mean difference
mg	Milligram
MI	Myocardial infarction
NYHA	New York Heart Association
PD	Peritoneal dialysis
PICOTS	Population, Intervention, Comparator, Outcome, Settings, Timing
P/I	Promising but inconclusive
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality-adjusted life year
RBC	Red blood cell
RCT	Randomized controlled trial
RR	Risk ratio
SF-36 (PF/VT)	Short Form-36 Health Survey (Physical Functioning/Vitality)
TEAE	Treatment-emergent adverse event
TIW	Three times weekly
TSAT	Transferrin saturation
US	United States
USPSTF	United States Preventive Services Task Force
WAC	Wholesale acquisition cost

Executive Summary

Anemia is common in patients with chronic kidney disease (CKD), and typically becomes more prevalent with decreasing hemoglobin (Hb) levels as CKD progresses from dialysis-independent CKD (DI-CKD) to dialysis-dependent CKD (DD-CKD).[1-4] Nearly all patients with DD-CKD have anemia that must be managed. Anemia in patients with CKD can be due to reduced production of erythropoietin by the kidneys, iron deficiency, inflammation, and the accumulation of uremic toxins that leads to shortened red blood cell (RBC) survival.[5-7]

Prior to the mid-1980s, blood transfusion was the main strategy for managing anemia in CKD. In the late 1980s, recombinant human erythropoietin was developed,[8] and the use of erythropoietin and related compounds collectively known as erythropoiesis-stimulating agents (ESAs) dramatically reduced the need for transfusions.[9] ESAs may be injected subcutaneously at home or infused during dialysis, and so different regimens may be chosen based on need for dialysis and/or intravenous (IV) iron, and based on whether patients receive home peritoneal dialysis, home hemodialysis, or in-center dialysis. Despite the association between anemia and higher mortality in uncontrolled studies, subsequent evidence based on multiple randomized controlled trials (RCTs) emerged and showed that correction of anemia and maintenance of Hb to near normal levels with ESAs increased mortality and cardiovascular events without consistently improving quality of life.[10-13]

Hypoxia-inducible factor prolyl hydroxylase (HIF-PH) inhibitors have emerged as a new class of orally-administered agents for the management of anemia in CKD. They induce considerably lower, but more consistent, erythropoietin levels compared to ESAs and it has been hypothesized that they could cause fewer adverse cardiovascular events than ESAs.[14,15] The HIF-PH inhibitor roxadustat (AstraZeneca) is under review by the Food and Drug Administration (FDA).[16]

In speaking with patients and patient organizations, we heard about the importance that patients place on autonomy and the ability to maintain activities of daily living. Most patients described their experiences with fatigue. We heard that among those patients with anemia, some feel better after their anemia is treated and some do not. We also heard concerns about becoming sensitized through transfusions, reducing the chance of finding an appropriate kidney for transplant.

ESAs and roxadustat can both be dose-adjusted to correct anemia to a given degree and reduce the need for transfusions,[17] although patients receiving ESAs frequently also need to receive IV iron. As such, a primary focus of our review looked at the relative safety of these therapies as assessed by all-cause mortality, myocardial infarction (MI), and stroke (the composite "MACE" in the roxadustat trials), and additional endpoints of hospitalization for unstable angina or heart failure ("MACE+").

In the DI-CKD population, we identified three key published Phase III randomized controlled trials (RCTs) of roxadustat[18-20] and one key unpublished Phase III RCT of roxadustat.[21] A pooled analysis of the placebo-controlled trials reported no statistically significant difference in all-cause mortality with roxadustat (hazard ratio [HR]: 1.06; 95% confidence interval [CI]: 0.91 to 1.23), however this included many patients no longer on treatment, which could bias toward no effect. A meta-analysis of relative risks (RRs) suggested a possible increase in mortality with roxadustat (RR: 1.15, 95% CI: 1.00 to 1.33), however discontinuations could have biased this result toward overestimating any such risk.[17] In support of this possibility, the HR for mortality on treatment was published for one trial and was 0.96, compared with a RR of 1.17 from that same trial.[20,22,23] In the trial comparing roxadustat with an ESA, there were no statistically significant differences in the risk of MACE (HR: 0.81, CI: 0.52 to 1.25), MACE+ (HR: 0.90, CI: 0.61 to 1.32), or all-cause mortality (HR: 0.83, CI: 0.50 to 1.38).[21]

In the DD-CKD population, we also identified four key unpublished Phase III RCTs comparing roxadustat with ESAs.[22,24-26] A pooled analysis of three of these trials reported that roxadustat was not different from ESAs in the risk of first MACE (HR: 0.96, CI: 0.82 to 1.13) and all-cause mortality (HR: 0.96, CI: 0.79 to 1.17), however roxadustat reduced the risk of MACE+ (HR: 0.85, CI: 0.74 to 0.98).[17] We used available data from all four trials to perform a meta-analysis of all-cause mortality and found no statistically significant difference (risk ratio [RR]: 1.05, CI: 0.88 to 1.26). The need for IV iron supplementation was reduced with roxadustat across all trials.

In summary, in the DI-CKD population, roxadustat reduces the need for transfusions compared to usual care, but we have substantial uncertainty about the effects of roxadustat on all-cause mortality and have rated the evidence *insufficient* ("*I*") for this comparison. Compared with ESAs, the confidence intervals around MACE and MACE+ include the possibilities of clinically important harms and benefits and, as such, we have rated the evidence *insufficient* (*I*) for this comparison as well. For similar reasons, in the DD-CKD population, we have *insufficient* evidence (*I*) for the comparison between roxadustat and ESAs.

Votes of the California Technology Assessment Forum (CTAF) at the Public Meeting on February 11, 2021 agreed with the above assessments: the CTAF Panel unanimously voted that evidence was not adequate to demonstrate to demonstrate the superiority of roxadustat over usual care in the DI-CKD population or to distinguish the net health benefit in comparison with ESAs in the DI- and DD-CKD populations.

In economic modeling, we assumed a placeholder price for roxadustat of $6,500 per year using analysts' estimates. In the DI-CKD population, given the lack of statistical significance, we assumed no difference in MACE+ events, and roxadustat slightly reduced lifetime costs with no effect on quality-adjusted life years (QALYs) or equal-value life years (evLYs) compared with ESAs. In the DD-CKD population, we used point estimates of individual MACE+ outcomes given the statistical significance of the composite. The increased all-cause mortality estimate resulted in fewer QALYs

and evLYs with roxadustat. Roxadustat treatment in the DD-CKD population had small reductions in lifetime costs both from a commercial and Medicare perspective, driven primarily by less time spent in CKD health states due to higher mortality rather than from improvements in patient outcomes.

The CTAF votes on potential other benefits and contextual considerations highlighted that roxadustat has a new mechanism of action and that its oral route of administration could improve real-world adherence compared with ESAs. CTAF also highlighted the large burden of illness of CKD.

There is currently insufficient evidence to compare roxadustat and ESAs. Roxadustat provides an oral option for treating anemia related to CKD and reduces the need for IV iron. Although it has been suggested to be a safer alternative to ESAs, the evidence does not currently confirm that conclusion. Cost effectiveness will depend on the manufacturer's price.

Themes and recommendations from the CTAF Public Meeting include:

- Given the level of uncertainty about the benefits versus harms and the long-term effect of using roxadustat compared to ESAs, we strongly suggest a mandate for a registry or other rapid and comprehensive post-marketing assessment.
- The manufacturer should not hold data in confidence from RCTs completed more than one to two years ago. The company has a responsibility to patients and clinicians to move these data into the public domain, to submit data rapidly for peer review in advance of regulatory approval, and to share these data in a transparent manner with groups seeking to assess the evidence to inform clinical practice and policy.
- If roxadustat gains regulatory approval, the manufacturer should price the drug in alignment with its demonstrated value, which at the current time is highly uncertain given the lack of clarity about overall mortality and cardiovascular outcomes. In this setting, with significant uncertainty of this magnitude, the manufacturer should set the price lower than treatments with more established evidence and wait until further evidence addresses the uncertainties before seeking a higher price.
- The manufacturer and researchers should avoid focusing primarily on Hb levels and the need for transfusion. Future research should expand outcomes measured to include patient-relevant outcomes such as quality of life, functional status, fatigue, overall cardiovascular events, and mortality in addition to the need for transfusion.

1. Background

Anemia is common in patients with chronic kidney disease (CKD), and hemoglobin (Hb) levels typically decline as CKD progresses.[1-3] The World Health Organization and the 2012 Kidney Disease Improving Global Outcomes guidelines define anemia as an Hb level of <12 g/dL in females and <13 g/dL in adult males, however this definition does not provide goals of treatment for different patient groups.[27,28] Anemia in patients with CKD can be due to reduced production of erythropoietin by the kidneys, iron deficiency, inflammation, and the accumulation of uremic toxins that leads to shortened red blood cell (RBC) survival.[5-7] Anemia causes many of the symptoms associated with CKD such as fatigue, depression, breathlessness, and reduced exercise tolerance. Anemia is also associated with increased morbidity, mortality, and hospitalizations.[29-32]

Decreased kidney function refers to a decrease in glomerular filtration rate (GFR), which is usually estimated using serum creatinine and one of several available equations.[33,34] This definition is widely accepted and used among patients, clinicians, researchers, and regulatory agencies. Patients who are diagnosed with CKD can be categorized into different stages according to the cause, their GFR (five G-stages: I, II, III, IV, and V), and the amount of albumin or protein in the urine (three A-stages: 1, 2, and 3). Additionally, patients with CKD can advance from being dialysis-independent (DI-CKD) to kidney failure (also known as end-stage kidney disease [ESKD]), which is defined as severely reduced kidney function or treatment with dialysis (dialysis-dependent [DD-CKD]), or transplantation. Risk factors for CKD include genetic or sociodemographic predisposition, or the presence of diseases that can initiate and worsen kidney disease such as diabetes and hypertension. African Americans and Hispanics are at increased risk of CKD.[35] The number of patients enrolled in the ESKD Medicare-funded program has increased from approximately 10,000 beneficiaries in 1973 to 703,243 as of 2015.[36]

In patients with DI-CKD, the prevalence of anemia increases with decline in kidney function and advancing stages of CKD.[1,3] For example, based on over 12,000 participants in the National Health and Nutrition Examination Survey, the prevalence of anemia increased from 8.4% at CKD stage G-I to 53.4% at CKD stage G-V.[4] Nearly all patients with DD-CKD have anemia that must be managed.

Prior to the mid-1980s, blood transfusion—with its attendant risks of iron overload, antibody formation against blood cell antigens, sensitization to renal transplant antigens, and transfusion-related infections—was the main strategy for managing anemia in CKD. In the late 1980s, recombinant human erythropoietin was developed,[8] and the use of erythropoietin and related compounds (epoetin alfa, epoetin beta, darbepoetin alfa, methoxy polyethylene glycol-epoetin beta; collectively known as erythropoiesis-stimulating agents [ESAs]) and subsequently biosimilars administered intravenously or subcutaneously dramatically reduced the need for transfusions.[9] However, despite the association between anemia and higher mortality in uncontrolled studies, subsequent evidence based on multiple randomized controlled trials (RCTs) emerged and showed

that correction of anemia and maintenance of Hb to near normal levels with ESAs increased mortality and cardiovascular events without consistently improving quality of life.[10-13] As a result, target Hb levels in patients with DD-CKD were reduced.[9]

Anemia management varies considerably depending on whether the patient has DI-CKD or DD-CKD and among different individuals. Patients who have DI-CKD, especially those who have advanced stages requiring more frequent treatment for their anemia, receive ESAs and intravenous (IV) iron if needed in outpatient clinics or infusion centers. Many of these patients receive long-acting ESAs as subcutaneous injections every two to four weeks. Patients who have DD-CKD receive ESAs and IV iron if needed during their dialysis session. This is especially true for those who receive in-center hemodialysis. For patients who receive home hemodialysis, a majority inject ESAs during their dialysis session or receive subcutaneous injections. However, for patients receiving peritoneal dialysis, some inject themselves with subcutaneous ESAs while others receive their ESAs and IV iron in dialysis centers either during their monthly visits or during other visits if more frequent injections are needed.

Hypoxia-inducible factor (HIF) is a transcription factor that regulates the expression of genes in response to reduced oxygen levels (hypoxia), including genes required for erythropoiesis and iron metabolism. At normal oxygen concentrations, a family of HIF prolyl hydroxylase (HIF-PH) enzymes hydroxylate the HIF-α subunit, resulting in its rapid degradation. HIF-PH inhibitors have emerged as a new class of orally-administered agents for the management of anemia in CKD. They induce considerably lower, but more consistent, erythropoietin levels compared to ESAs. As such, it has been hypothesized that they could cause fewer adverse cardiovascular events than ESAs. The HIF-PH inhibitor roxadustat (AstraZeneca) is under review by the Food and Drug Administration (FDA).[16] Roxadustat is the focus of this report. Roxadustat is administered orally three times per week. Three other HIF-PH inhibitors, vadadustat, daprodustat, and molidustat, are undergoing Phase II and III clinical trials in the United States (US).

2. Patient and Caregiver Perspectives

ICER engaged with patients with CKD (DI-CKD, DD-CKD, and post-transplant), caregivers, representatives from professional and advocacy organizations, and clinical experts to understand the specific challenges associated with ongoing management of anemia in CKD from the patient perspective. Patients described that while DI-CKD may not initially change their day-to-day experience, reaching kidney failure and beginning dialysis has important effects on quality of life. We heard that among patients with DD-CKD, home dialysis is less disruptive to daily life than in-center dialysis. In addition, we heard about the importance that patients place on autonomy and the ability to maintain activities of daily living. However, this can vary among individuals depending on their baseline activity level and other commitments including work and family responsibilities.

Most patients described their experiences with fatigue. We heard that among those patients with anemia, some feel better after their anemia is treated and some do not. Patients described their anemia management as a continued effort to find the right treatment with ESAs and iron supplements. One patient stated, "It was something that I really had to manage because it really affected my energy level… I had to push my way through it or contact my dialysis nurse just to ask, 'How can I better manage this?'"

Patients and clinicians highlighted the importance of avoiding blood transfusion to decrease antibody formation and sensitization. One patient noted, "Our concern is if you're doing transfusions and putting someone at a disadvantage of receiving a transplant." Patients and providers described the importance of other patient-centered outcomes such as cardiovascular events. It was evident through our discussions that there exists frustration among the patient community about lack of reporting on outcomes that matter to patients.

In addition, it was noted that the choice of specific ESA is dependent on multiple factors that are typically not patient-related. Specific ESA products are used by different dialysis providers. Also, ESA availability varies for inpatient versus outpatient care depending on the formulary. Furthermore, different ESAs are used differentially for DI-CKD or DD-CKD based on market agreements. However, patients and clinicians did not mention specific preferences except for ease of administration of ESAs that are longer acting and require less frequent injections.

Patients and advocacy groups voiced a desire for more choices related to anemia management, particularly for patients who experience side effects with ESAs, those who do not tolerate treatment with ESAs, those who are not responsive or unable to achieve target Hb levels with ESAs, and those for whom ESAs are contraindicated (e.g., patients with active cancer with a chance of cure and venous thromboembolism). We heard that an oral option will likely be more important for DI-CKD and home dialysis patients, especially for patients receiving peritoneal dialysis where an oral treatment could reduce the need for injections. We also learned that particularly for patients

receiving in-center hemodialysis, an infused option included in dialysis is likely easier than taking an additional oral medication.

Advocacy groups highlighted the importance of supporting innovation and new treatment options and raised concerns that the Medicare bundled payment system could stifle innovation. Patients and advocacy groups raised concerns about the affordability of medications for patients with DI-CKD.

3. Comparative Clinical Effectiveness

3.1. Methods Overview

Procedures for the systematic literature review assessing the evidence on roxadustat for anemia in DI-CKD and DD-CKD are detailed in the Report Supplement.

Scope of Review

We reviewed the clinical effectiveness of roxadustat for the treatment of anemia in adults with DI-CKD (stages III, IV, and V) in comparison with usual care (estimated by the placebo arm of clinical trials) and in comparison with ESAs, and in adults with DD-CKD in comparison with ESAs. Because ESAs have been shown to have similar efficacy and safety profiles,[37] they are assumed to be equivalent in this report. We looked for evidence on patient-important outcomes including the need for blood transfusion, mortality, cardiovascular events, and health-related quality of life (HRQoL), but also on laboratory measures of anemia. The full scope of the review is detailed in the Report Supplement.

Evidence Base

Note that in the key trials of roxadustat in both populations below, cardiovascular outcomes were assessed by two composite endpoints: MACE (major adverse cardiovascular events), defined as all-cause mortality (**not** cardiovascular mortality), myocardial infarction (MI), or stroke; and MACE+, defined as MACE or unstable angina requiring hospitalization or congestive heart failure requiring hospitalization.

DI-CKD

A total of 12 references relating to two RCTs comparing roxadustat to darbepoetin alfa[21,38] and eight RCTs comparing roxadustat to placebo[18-20,22,26,39-43] met our inclusion criteria. A detailed description of these RCTs is included in the Report Supplement.

Key Trials of Roxadustat in the DI-CKD Population

We identified four Phase III, multicenter RCTs of roxadustat in DI-CKD.[18-21] ALPS, ANDES, and OLYMPUS have been published, and additional data for these trials and DOLOMITES was obtained from a clinical trial report, conference presentation, investor presentation, a pre-approval Academy of Managed Care (AMCP) dossier, and the clinicaltrials.gov database (ALPS and OLYMPUS only).

The DOLOMITES trial was a multicenter, Phase III, open-label RCT conducted primarily in Europe that compared the efficacy and safety of roxadustat to darbepoetin alfa in adults with DI-CKD stages

III, IV, and V.[21] In contrast, the ALPS, ANDES, and OLYMPUS trials were global, multicenter Phase III, double-blind RCTs that compared the efficacy and safety of roxadustat to placebo in these groups.[26,22] The RCTs had similar inclusion and exclusion criteria and baseline characteristics (see Table 3.1).

DD-CKD

A total of 11 references relating to six RCTs in stable DD-CKD,[22,25,40,42,44-46] two RCTs in incident and stable DD-CKD,[22,26] and one RCT in incident DD-CKD[22,24] met our inclusion criteria. A detailed description of these RCTs is included in the Report Supplement. The key RCTs defined incident and stable DD-CKD as receiving dialysis for two weeks to ≤4 months and >4 months, respectively, prior to randomization.

Key Trials of Roxadustat in the DD-CKD Population

We identified four Phase III, multicenter RCTs of roxadustat in DD-CKD.[22,24-26] All RCTs are currently unpublished, and data for these studies was obtained from a clinical trial report, conference presentation, investor presentation, a pre-approval AMCP dossier, and the clinicaltrials.gov database (PYRENEES and ROCKIES only).

HIMALAYAS, ROCKIES, and SIERRAS were global, multicenter, Phase III, open-label RCTs that compared the efficacy and safety of roxadustat to epoetin alfa in adults with incident DD-CKD (HIMALAYAS) or incident DD-CKD and stable DD-CKD (ROCKIES and SIERRAS).[22,24,26] The PYRENEES trial was a multicenter, Phase III, open-label RCT conducted in Europe that compared the safety and efficacy of roxadustat to darbepoetin alfa and epoetin alfa (most results were presented in a pooled ESA treatment arm) in adults with stable DD-CKD.[22,25] Mean Hb at baseline was highest in PYRENEES, followed by SIERRAS, ROCKIES, and HIMALAYAS (see Table 3.1 on the following page).

Table 3.1. Overview of Key Trials

Trials (No. of Patients)	Population	Primary Endpoint	Treatment Arms	Key Baseline Characteristics
DI-CKD				
DOLOMITES (616)	DI-CKD	Hb response* during the first 24 weeks of treatment without rescue therapy	I: Roxadustat TIW† C: Darbepoetin alfa	Mean age: 66 Mean Hb: 9.55 g/dL Iron replete: 54% CRP >ULN: 37%
ALPS (594)	DI-CKD	Mean CFB in Hb averaged over weeks 28-52	I: Roxadustat 70 or 100 mg TIW‡ C: Placebo	Mean age: 61 Mean Hb: 9.09 g/dL Iron replete: 53% CRP >ULN: 35%
ANDES (922)	DI-CKD	Mean CFB in Hb averaged over weeks 28-52	I: Roxadustat 70 or 100 mg TIW‡ C: Placebo	Mean age: 65 Mean Hb: 9.10 g/dL Iron replete: 60% CRP >ULN: 26%
OLYMPUS (2781)	DI-CKD	Mean CFB in Hb averaged over weeks 28 to 52	I: Roxadustat 70 mg TIW C: Placebo	Mean age: 62 Mean Hb: 9.10 g/dL Iron Replete: 58% CRP >ULN: 16%
DD-CKD§				
HIMALAYAS (1043)	Incident DD-CKD	Mean CFB in Hb averaged over weeks 28-52	I: Roxadustat 70 or 100 mg TIW‡ C: Epoetin alfa	Mean age: 54 Incident DD-CKD: 100% Mean Hb: 8.45 g/dL CRP >ULN: 52%
PYRENEES (836)	Stable DD-CKD	Mean CFB in Hb averaged over weeks 28-52	I: Roxadustat 70 or 100 mg TIW# C: Epoetin alfa or darbepoetin alfa	Mean age: 61 Incident DD-CKD: 0% Mean Hb: 10.77 g/dL CRP >ULN: NR
ROCKIES (2133)	Incident and stable DD-CKD	Mean CFB in Hb averaged over weeks 28-52	I: Roxadustat 70, 100, 150, or 200 mg TIW# C: Epoetin alfa	Mean age: 54 Incident DD-CKD: 20% Mean Hb: 9.10 g/dL CRP >ULN: NR
SIERRAS (741)	Incident and stable DD-CKD	Mean CFB in Hb averaged over weeks 28-52	I: Roxadustat 70, 100, 150, or 200 mg TIW# C: Epoetin alfa	Mean age: NR Incident DD-CKD: 10% Mean Hb: 10.25 g/dL CRP >ULN: 49%

CFB: change from baseline, CKD: chronic kidney disease, CRP: C-reactive protein, C: comparison, DD: dialysis-dependent, DI: dialysis-independent, ESAs: erythropoiesis-stimulating agents, g/dL: grams per deciliter, Hb: hemoglobin, I: intervention, mg: milligram, No.: number, NR: not reported, TIW: three times weekly, ULN: upper limit of normal

*Defined as Hb ≥11.0 g/dL and an Hb increase from baseline of 1.0 g/dL in patients with baseline Hb >8.0 g/dL, or an increase of ≥2.0 g/dL in patients with baseline Hb ≤8.0 g/dL.

†Weight-based starting dose not reported.

‡Weight-based starting dose.

§No key trials reported iron-repletion status.

#Starting dose varied based on weight and prior ESA use.

3.2. Results

Clinical Benefits of Roxadustat

The clinical benefits of roxadustat in the key RCTs are first detailed in the DI-CKD population, followed by the DD-CKD population. Additional outcomes and results from other RCTs are described in the Report Supplement.

DI-CKD

Cardiovascular Safety

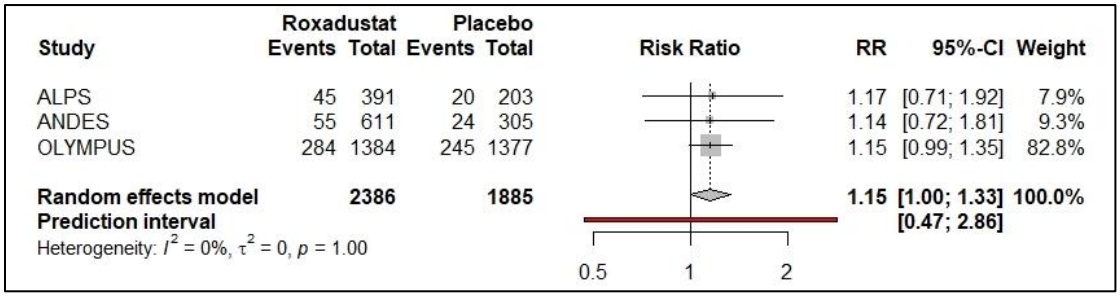
As described above, the key RCTs were designed with Hb as the primary endpoint; thus, the number of cardiovascular events was low (see Evidence Table 11).

DOLOMITES RCT (roxadustat vs. darbepoetin alfa): At the time of this report, adjudicated cardiovascular events were reported in a non-confirmatory analysis.[21] There were no significant differences in the risk of MACE (HR: 0.81; 95% CI: 0.52 to 1.25), MACE+ (HR: 0.90; 95% CI: 0.61 to 1.32), or all-cause mortality (HR: 0.83; 95% CI: 0.50 to 1.38) during the safety emergent period. Additionally, there were no significant differences in the risk of MI, stroke, unstable angina requiring hospitalization, or congestive heart failure requiring hospitalization (see Table D7 in the Report Supplement).

ALPS, ANDES, and OLYMPUS RCTs (roxadustat vs. placebo): A pooled analysis of the intention-to-treat populations of ALPS, ANDES, and OLYMPUS reported that roxadustat was not significantly different from placebo in the risk of MACE (HR: 1.08; 95% CI: 0.94 to 1.24), MACE+ (HR: 1.04; 95% CI: 0.91 to 1.18), and all-cause mortality (HR: 1.06; 95% CI: 0.91 to 1.23) during the study period.[17]

However, the HR for all-cause mortality reported above was based on all deaths during the study period, including deaths in patients no longer on therapy. At the time of this report, the data from primary studies used to pool the HR for this outcome are unavailable. Thus, we also performed a meta-analysis of available data for all-cause mortality.[19,20,22,23] As seen in Report Supplement Figure D6, the meta-analysis found an increased risk of all-cause mortality with roxadustat of borderline statistical significance (risk ratio [RR]: 1.15; 95% CI: 1.00 to 1.33; I^2=0%). While all-cause mortality reported for ALPS appears to have been up to 28 days after the last dose of study drug (available sources currently disagree slightly on these numbers), all-cause mortality reported for OLYMPUS was up to and including the end of study visit or date of last contact or withdrawal of consent. The timepoint in which all-cause mortality was reported for ANDES is unclear at the time of this report. The reported HR for mortality up to 28 days after the last dose of study drug was 0.96; 95% CI: 0.53 to 1.74,[20] which is substantially lower than the RR of 1.17; this suggests that the RR calculations may be overestimating risk that takes into account time of exposure to therapy and time to events.

Figure 3.1. Meta-Analysis of All-Cause Mortality for ALPS*, ANDES, and OLYMPUS



95% CI: 95% confidence interval, I2: I-squared, RR: risk ratio, τ2: between-study-variance estimator
*We note disagreement among sources.

HRQoL

At the time of this report, only Short Form (SF)-36 Health Survey results were reported for DOLOMITES, while results from SF-36 and other assessments were reported for ALPS, ANDES, and OLYMPUS. Results for SF-36 are presented here, where higher scores indicate better quality of life. Results for the remaining assessments are presented in the Report Supplement; however, none of the results were clinically meaningful based on validated minimum clinically important differences (MCIDs).

DOLOMITES RCT (roxadustat vs. darbepoetin alfa): Patients receiving roxadustat had a significant decline in SF-36 Physical Functioning (PF) sub-score averaged over weeks 12 to 28 (least squares means [LSM] difference: -1.28; 95% CI: -2.42 to -0.15) compared with those on darbepoetin alfa.[21] However, this difference did not exceed the MCID of 3 to 5 points.[47] There was no significant difference between roxadustat and darbepoetin alfa in mean change from baseline (CFB) in SF-36 Vitality (VT) sub-score averaged over weeks 12 to 28 (LSM difference: -0.46; 95% CI: -1.66 to 0.74).[21]

ALPS, ANDES, and OLYMPUS RCTs (roxadustat vs. placebo): A pooled analysis of these RCTs reported a significant increase in mean CFB in SF-36 PF sub-score (LSM difference: 0.53; 95% CI: 0.05 to 1.01) and mean CFB in SF-36 VT sub-score (LSM difference: 0.96; 95% CI: 0.44 to 1.47) at 12 weeks with roxadustat compared to placebo.[48] However, MCIDs of 3 to 5 points were not reached in SF-36 PF or VT sub-scores in the pooled analysis.[47] Further, we performed meta-analyses of these outcomes averaged over weeks 12 to 28 reported for ALPS, ANDES, and OLYMPUS.[18,20,49] The meta-analyses found no significant differences in SF-36 PF sub-score (mean difference [MD]: 0.55; 95% CI: -0.31 to 1.40) or SF-36 VT sub-score (MD: 0.75; 95% CI: -0.37 to 1.86) with roxadustat compared to placebo. See Figure D7 and Figure D8 in the Report Supplement for additional details. Because there were no significant differences in these endpoints averaged over weeks 12 to 28 in individual RCTs, it is unclear if the differences reported for the pooled analysis would also lack statistical significance at later timepoints. Further, in ALPS, there was no significant difference in mean CFB in SF-36 Physical Component sub-score averaged over weeks 12 to 28 with roxadustat compared to placebo (LSM difference: 0.37; 95% CI: -0.65 to 1.40).[23]

Rescue Therapy

DOLOMITES RCT (roxadustat vs. darbepoetin alfa): Data regarding a composite rescue therapy endpoint of blood transfusion, IV iron supplementation, and ESA treatment was unavailable at the time of this report. The risk of IV iron supplementation was significantly reduced with roxadustat compared to darbepoetin alfa in the first 36 weeks (HR: 0.45; 95%: CI: 0.26 to 0.78).

ALPS, ANDES, and OLYMPUS RCTs (roxadustat vs. placebo): In a pooled analysis of these RCTs, the risk of rescue therapy (HR: 0.19; 95% CI: 0.16 to 0.23) and blood transfusion (HR: 0.26; 95% CI: 0.21 to 0.32) in the first 52 weeks was significantly reduced with roxadustat compared to placebo.[17]

Anemia

DOLOMITES RCT (roxadustat vs. darbepoetin alfa): Mean CFB in Hb averaged over weeks 28 to 36 was not significantly different between the two groups (LSM difference: 0.02; 95% CI: -0.13 to 0.16).[21]

ALPS, ANDES, and OLYMPUS RCTs (roxadustat vs. placebo): We performed a meta-analysis on the primary outcome of mean CFB in Hb averaged over weeks 28 to 52. Roxadustat significantly increased Hb compared to placebo (MD: 1.63 g/dL; 95% CI: 0.98 to 2.27). See Report Supplement Figure D9 for additional details.

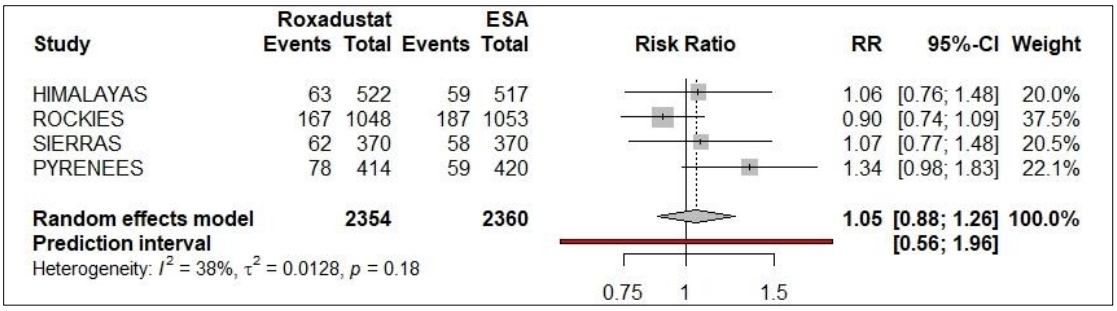
DD-CKD

Cardiovascular Safety

As described previously, the key RCTs were designed with Hb as the primary endpoint; thus, the number of cardiovascular events was low (see Evidence Table 26). Further, at the time of this report, no key RCTs reported adjudicated cardiovascular events.

A pooled analysis of an on-treatment analysis of HIMALAYAS, ROCKIES, and SIERRAS reported that roxadustat was not different from epoetin alfa in the risk of first MACE (HR: 0.96; 95% CI: 0.82 to 1.13) and all-cause mortality (HR: 0.96; 95% CI: 0.79 to 1.17) in the first 52 weeks.[17] However, the risk of MACE+ was reduced with roxadustat compared to epoetin alfa (HR: 0.86; 95% CI: 0.74 to 0.98).[17] Notably, the number of deaths reported in the individual RCTs exceeds that of the pooled analysis, and the pooled analysis did not include the fourth key RCT (PYRENEES).[22] Thus, we performed a meta-analysis of all-cause mortality reported for all four key RCTs (HIMALAYAS, PYRENEES, ROCKIES, and SIERRAS). As seen in Figure 3.2, the meta-analysis found no significant difference between roxadustat and ESAs (RR: 1.05; 95% CI: 0.88 to 1.26). These results should be interpreted with caution as the timepoints in which cardiovascular safety events were reported in the key RCTs are unclear.

Figure 3.2. Meta-Analysis of All-Cause Mortality in HIMALAYAS, PYRENEES, ROCKIES, and SIERRAS



95% CI: 95% confidence interval, ESA: erythropoiesis-stimulating agent, I^2: I-squared, RR: risk ratio, τ^2: between-study-variance estimator

HRQoL

At the time of this report, only PYRENEES assessed HRQoL. Statistical values were only reported for SF-36 and are described below. Results from the remaining assessments are detailed in the Report Supplement.

There were no significant differences in mean CFB in SF-36 PF sub-score (LSM difference: 0.21; 95% CI: -0.65 to 1.06), SF-36 VT sub-score (LSM difference: 0.86; 95% CI: -0.12 to 1.83), or SF-36 Physical Component sub-score (LSM difference: 0.52; 95% CI: -0.21, 1.25) averaged over weeks 12 to 28 with roxadustat compared to ESAs.[49] Notably, a MCID of 3 to 5 points was not reached in these assessments.[47]

Rescue Therapy

In PYRENEES, there was no significant difference in the risk of rescue therapy at the end of treatment (up to week 104) with roxadustat compared to ESAs (HR: 0.98; 95% CI: 0.66 to 1.46).[25] Similar results for rescue therapy were reported for ROCKIES in the first 52 weeks (HR: 0.83; 95% CI: 0.64 to 1.07).[22]

A pooled analysis of HIMALAYAS, ROCKIES, and SIERRAS reported a significant reduction in the risk of blood transfusion with roxadustat compared to epoetin alfa during treatment (HR: 0.82; 95% CI: 0.679 to 0.997).[17]

All key RCTs reported a significant reduction in mean monthly IV iron use (see Table D10 in the Report Supplement), and in PYRENEES, the risk of IV supplementation use at the end of treatment (up to 104 weeks) was significantly reduced with roxadustat compared to ESAs (HR: 0.37; 95% CI: 0.29 to 0.47).[22,50]

Anemia

We performed a meta-analysis on the primary outcome of mean CFB in Hb averaged over weeks 28 to 52 in HIMALAYAS, PYRENEES, ROCKIES, and SIERRAS. The summary estimate in CFB between roxadustat and ESAs was 0.23 g/dL (95% CI: -0.04 to 0.50). See Report Supplement Figure D15 for additional details.

Harms

The current package insert for roxadustat in Japan warns that roxadustat may cause serious thromboembolism, including cerebral infarction, MI, and pulmonary embolism, with a possible fatal outcome.[51] Cardiovascular safety events in the key RCTs are discussed above for the DI and DD-CKD populations.

DI-CKD

DOLOMITES RCT (roxadustat vs. darbepoetin alfa): Most treatment-emergent adverse events (TEAEs) were of mild-to-moderate severity (see Evidence Table 14).[21] The most commonly reported TEAEs included kidney failure, hypertension, decrease in eGFR, and peripheral edema. The incidence of any TEAE was marginally lower with roxadustat compared to darbepoetin alfa (91.6% vs. 92.5%, respectively) while the incidence of serious TEAEs was higher with roxadustat (64.7% vs. 61.8%, respectively). Further, the incidence of discontinuation due to TEAEs was higher with roxadustat compared to darbepoetin alfa (7.7% vs. 3.8%, respectively). Serious adverse events reported included all-cause mortality and cardiovascular events, which are presented above.

ALPS, ANDES, and OLYMPUS RCTs (roxadustat vs. placebo): Most TEAEs were of mild-to-moderate severity (see Evidence Table 14).[22] The most commonly reported TEAEs included kidney failure, decrease in eGFR, nausea, hyperkalemia, and hypertension.[22] We conducted a meta-analysis of any TEAE for ALPS and ANDES and a meta-analysis of discontinuation due to adverse events for ALPS and OLYMPUS. There were no significant differences in the risk of any TEAE with roxadustat compared to placebo (see Table D11 and Figure D16 in the Report Supplement). The incidence of serious TEAEs was higher with roxadustat compared to placebo. We also conducted a meta-analysis of discontinuation due to adverse events for ALPS and OLYMPUS, and the risk of discontinuation due to adverse events was significantly greater with roxadustat compared to placebo (RR: 1.51; 95% CI: 1.10 to 2.06; see Figure D17 in the Report Supplement). Serious adverse events reported included all-cause mortality and cardiovascular events, which are presented above.

DD-CKD

Most TEAEs were of mild-to-moderate severity, and the most commonly reported TEAEs included nausea, diarrhea, hyperkalemia, and hypertension (see Evidence Table 29).[22] We conducted meta-analyses of any TEAE and serious TEAEs for HIMALAYAS, PYRENEES, and SIERRAS and a meta-

analysis of discontinuation due to adverse events for HIMALAYAS, PYRENEES, and ROCKIES. There were no significant differences in the risk of any TEAE or serious TEAE with roxadustat compared to ESAs (see Figure D18 and Figure D19 in the Report Supplement); however, the risk of discontinuation due to adverse events was significantly greater with roxadustat compared to ESAs (RR: 1.87; 95% CI: 1.34 to 2.63; see Figure D20 in the Report Supplement). Serious adverse events reported included all-cause mortality and cardiovascular events, which are presented above.

Subgroup Analyses and Heterogeneity

We did not identify any RCTs that assessed the impact of roxadustat on subgroups of patients with cardiovascular disease or cancer, as these patients were excluded from the RCTs (see Evidence Table 1 and Evidence Table 17). We describe the subgroups of patients defined by iron and inflammation states and those with incident DD-CKD below.

DI-CKD

Subgroups Defined by Iron and Inflammation States

ALPS, ANDES, and OLYMPUS RCTs (roxadustat vs. placebo): We identified ten references for subgroup analyses of the key RCTs and pooled analysis.[17,19,20,22,48,52-56] The results demonstrated significant improvements with roxadustat compared to placebo (on use of rescue therapy, blood transfusion, IV iron supplementation, change in Hb, and change in transferrin saturation) with roxadustat compared to placebo regardless of iron states (see Evidence Table 6, Evidence Table 7, Evidence Table 34, and Evidence Table 37). Further, the results showed significant improvements in change in Hb with roxadustat compared to placebo regardless of inflammation states, though the differences reported in HRQoL did not meet MCIDs (see Evidence Table 34 and Evidence Table 37). Qualitatively, there were no subgroup effects based on iron or inflammation states.

Subgroups Defined by Stages of CKD: G-Stages III, IV, and V

ANDES RCT (roxadustat vs. placebo): We identified one reference for subgroup analyses of CKD G-stages III, IV, and V.[18] The results demonstrated significant improvements with roxadustat compared to placebo on change in Hb regardless of CKD G-stage (see Evidence Table 7). The treatment difference estimate was largest in CKD G-stage V followed by IV with non-overlapping confidence intervals between results from CKD G-stage III and V.

DD-CKD

Subgroups Defined by Iron and Inflammation States

We identified three references for subgroup analyses of HIMALAYAS, ROCKIES, SIERRAS, and a pooled analysis of these RCTs.[22,24,57] The results demonstrated that roxadustat offers significant

improvements compared to epoetin alfa (on change in Hb) regardless of iron and inflammation states (see Evidence Table 24 and Evidence Table 35). Qualitatively, there were no subgroup effects based on iron or inflammation states. However, comparable data for PYRENEES are unavailable at the time of this report.

Other RCTs demonstrated similar trends regardless of inflammation state, though statistical values were not reported.[40,44]

Incident-Dialysis Subgroup

We identified two references for subgroup analyses of incident DD-CKD patients.[58,59] As described above, the HIMALAYAS RCT only included incident DD-CKD patients, while in ROCKIES and SIERRAS, 10% and 20% of the enrolled patients, respectively, were incident DD-CKD patients. A pooled analysis of HIMALAYAS and the incident DD-CKD subgroups of ROCKIES and SIERRAS showed the risk of MACE and MACE+ was significantly reduced with roxadustat compared to placebo; however, there was no significant difference in the risk of all-cause mortality (see Evidence Table 39). Because these endpoints were not available for the stable DD-CKD subgroups of ROCKIES and SIERRAS at the time of this report, we were unable to assess whether these results differ. However, as mentioned previously, in a pooled analysis of HIMALAYAS, ROCKIES, and SIERRAS, only the risk of MACE+ was significantly reduced with roxadustat compared to epoetin alfa.[17]

Uncertainty and Controversies

In all the major included trials, patients with known New York Heart Association Class III or IV congestive heart failure, MI, acute coronary syndrome, stroke, seizure, or a thrombotic/thromboembolic event within 12 weeks, and uncontrolled hypertension were excluded from the trials. This limits the generalizability of the results to many patients with CKD. Some of these populations were identified by clinical experts as subgroups of particular interest given known harms from ESAs in these populations.

For patients with DI-CKD, the data available for this report make it uncertain how best to estimate the effect of roxadustat on mortality, and perhaps MACE, compared to usual care. There were large numbers of patients discontinuing therapy in both the active and placebo arms of the clinical trials, and this makes a time-to-event analysis most likely to be informative. However, for two of the trials we only have time-to-event analyses for the entire study period, and this means that many patients were included who were no longer on active treatment. As such, harms of treatment could be diluted, biasing results toward no effect. Estimates of relative risk are possible for the patients on active treatment, but higher discontinuation rates in the placebo arms of the trials mean that these patients had less time for adverse events and so the calculated RRs may overestimate harms of active treatment. The one trial (ALPS) in which we had both RR and HR for mortality while on treatment suggest such an overestimation by the RR.

For patients with DD-CKD, available pooled estimates of cardiovascular outcomes exclude results from the PYRENEES trial referencing differences in the comparator (two different ESA products were used in the trial, whereas, in the three pooled trials [HIMALAYAS, ROCKIES, and SIERRAS] only epoetin alfa was used). ESAs have been shown to have similar efficacy and safety profiles.[37] We believe results from PYRENEES should be included in the pooled safety and efficacy analyses.

Given changes to recommended Hb targets and modifications in practice over the years, we felt that it was not possible to use older trials to inform a network meta-analysis comparing ESAs and roxadustat.

It is uncertain whether the increases in cardiovascular risk seen in older trials of ESAs were due to the higher target Hb levels achieved or toxicity from higher doses of the ESAs. The issue of whether roxadustat has lower cardiovascular risk, similar risk, or higher risk than ESAs, and whether this varies by CKD status (DI, incident DD, or stable DD) is uncertain. Additional information on the individual components of MACE and MACE+ could help clarify the results. This is of critical importance to patients and clinicians not just in assessing the relative benefits of the therapies, but in understanding whether achieving normal Hb levels in patients with CKD is safe.

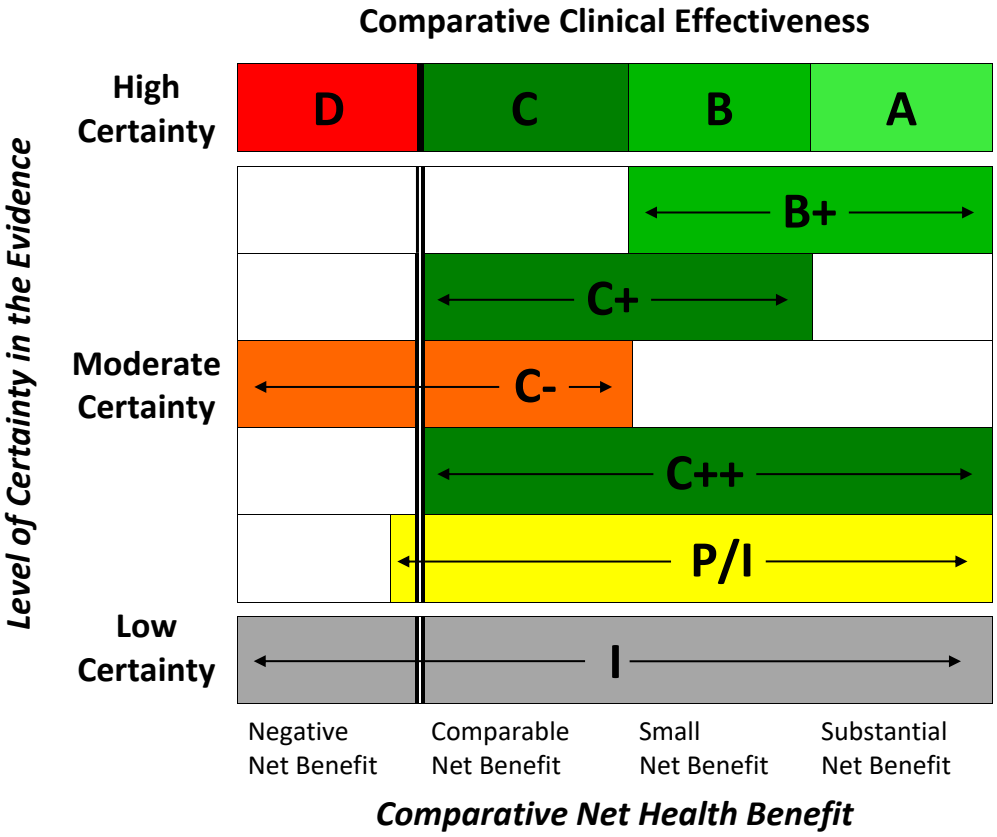
A potentially important subgroup that has been evaluated in the DD-CKD trials is the incident DD-CKD group. The results of the pooled analysis of HIMALAYAS and the incident DD-CKD subgroups of ROCKIES (20%) and SIERRAS (10%) showed a significant reduction in the risk of MACE and MACE+. The between-studies comparison rather than within-studies comparison drove the pooled effect estimate for MACE and MACE+ in the incident DD-CKD subgroup. Additionally, the lack of reported data about the stable DD-CKD in ROCKIES and SIERRAS prohibited pooling MACE and MACE+ in the stable DD-CKD, which theoretically could have had an increase in the risk of these outcomes in the roxadustat versus ESA group. As such, we are uncertain about a subgroup effect.

We acknowledge the differences in the use of rescue therapy between the treatment arms in the trials in which ESAs were used as part of the rescue therapy for the roxadustat arm. However, the limited available data hinder further exploration of the impact of these differences and the potential associated biases. Additionally, the lack of reported data on quality of life and functional status further limits our ability to assess the impact of roxadustat on these outcomes.

3.3. Summary and Comment

An explanation of the ICER Evidence Rating Matrix (Figure 3.2) is provided here.

Figure 3.2. ICER Evidence Rating Matrix



A = "Superior" - *High certainty of a substantial (moderate-large) net health benefit*
B = "Incremental" - *High certainty of a small net health benefit*
C = "Comparable"- *High certainty of a comparable net health benefit*
D= "Negative"- *High certainty of an inferior net health benefit*
B+= "Incremental or Better" – *Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+ = "Comparable or Incremental" - *Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit*
C- = "Comparable or Inferior" – *Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit*
C++ = "Comparable or Better" - *Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I = "Promising but Inconclusive" *- Moderate certainty of a small or substantial net health benefit, small likelihood of a negative net health benefit*
I = "Insufficient" – *Any situation in which the level of certainty in the evidence is low*

Roxadustat Compared with ESAs (i.e., Darbepoetin Alfa) in the DI-CKD Population

The key trial (DOLOMITES) has not been published, and long-term evidence is not yet available. Available data suggest that roxadustat does not significantly increase Hb, reduce the risk of cardiovascular safety events, or lead to clinically meaningful differences in HRQoL compared to darbepoetin alfa. Roxadustat does reduce the use of IV iron supplementation.

Although available data on all-cause mortality found no statistically significant difference between roxadustat and darbepoetin alfa (HR: 0.83; 95% CI: 0.50 to 1.38), given the high baseline risk of mortality in this population (11% baseline mortality in the control arm of DOLOMITES), the results indicate that the absolute effect of roxadustat on DI-CKD populations could range from five fewer to four additional deaths per 100 patients treated (timeframe up to two years of treatment). These numbers include a potentially large benefit to large harm. Given this uncertainty, we rate the evidence comparing roxadustat to ESAs as *insufficient* (*"I"*).

Roxadustat Compared with Usual Care (Estimated by the Placebo Arms of Clinical Trials) in the DI-CKD Population

While two key trials, ANDES and OLYMPUS, have been published, ALPS has not, and data for most endpoints are only available in pooled analyses. Long-term evidence is not yet available. Available data suggest that roxadustat significantly increases Hb compared to placebo without increasing the risk of cardiovascular safety events or generally leading to clinically meaningful differences in HRQoL. Roxadustat reduces the need for blood transfusions, rescue therapy with ESAs, and the use of IV iron.

A pooled analysis of the placebo-controlled trials reported no statistically significant difference in all-cause mortality with roxadustat (HR: 1.06; 95% CI: 0.91 to 1.23), however this included many patients no longer on treatment, which could bias toward no effect. A meta-analysis of relative risks (RRs) suggested a possible increase in mortality with roxadustat (RR: 1.15, 95% CI: 1.00 to 1.33), however, discontinuations could have biased this result toward overestimating any such risk. We are left with substantial uncertainty about the best estimate of mortality with roxadustat. Given the high baseline risk of mortality in this population (15% based on baseline mortality in the control arms of the included RCTs), the results indicate that the absolute effect of roxadustat on DI-CKD populations could range from one fewer to five additional deaths per 100 patients (timeframe between one and four and a half years of treatment). Given this uncertainty, we rate the evidence comparing roxadustat to usual care as *insufficient* (*I*).

Roxadustat Compared with ESAs (i.e., Darbepoetin Alfa and Epoetin Alfa) in the DD-CKD Population

The key trials (HIMALAYAS, PYRENEES, ROCKIES, and SIERRAs) have not been published, and data for most endpoints are only available in pooled analyses that exclude PYRENEES. Long-term evidence is not yet available. Available data suggest that roxadustat does not significantly increase Hb, reduce the risk of MACE or all-cause mortality, or lead to clinically meaningful differences in HRQoL compared to ESAs. However, roxadustat reduced the risk of MACE+ in a pooled analysis that excluded PYRENEES. Roxadustat appears to reduce the use of blood transfusion and IV iron supplementation.

Although available data on all-cause mortality suggest no statistically significant difference between roxadustat and ESAs (HR: 1.05; 95% CI: 0.88 to 1.26), given the high baseline risk of mortality in this population (15% baseline mortality in the control arms of the included RCTs), the results indicate that the absolute effect of roxadustat on DD-CKD populations could range from two fewer to four additional deaths per 100 patients treated (timeframe between one and four years of treatment). Given this uncertainty, we rate the evidence comparing roxadustat to ESA as *insufficient* (*I*).

Table 3.2. Evidence Ratings

Treatment	Comparator	Evidence Rating
DI-CKD		
Roxadustat	ESAs (i.e., darbepoetin alfa)	Insufficient (I)
	Usual care (estimated by the placebo arms of clinical trials)	Insufficient (I)
DD-CKD		
Roxadustat	ESAs (i.e., epoetin alfa and darbepoetin alfa)	Insufficient (I)

DI: dialysis-independent, DD: dialysis-dependent, ESAs: erythropoiesis-stimulating agent

CTAF Votes

During ICER Public Meetings, the CTAF Panel deliberates and votes on key questions related to the systematic review of the clinical evidence, an economic analysis of the applications of treatments under examination, and the supplementary information presented. Panel members are not pre-selected based on the topic being addressed and are intentionally selected to represent a range of expertise and diverse perspectives.

Acknowledging that any judgment of evidence is strengthened by real-life clinical and patient perspectives, subject matter experts are recruited for each meeting topic and provide input to CTAF Panel members before the meeting to help clarify their understanding of the different interventions being analyzed in the evidence review. The same clinical experts serve as a resource to the CTAF Panel during their deliberation and help to shape recommendations on ways the evidence can apply to policy and practice.

Voting results for comparative clinical effectiveness may be found below; results for potential other benefits and contextual considerations and long-term value for money may be found in Section 5 and Section 6, respectively.

Table 3.3. CTAF Votes on Comparative Clinical Effectiveness Questions

Question	Yes	No
Given currently available evidence, in patients who have DI-CKD, is the evidence adequate to demonstrate that the net health benefit of roxadustat is superior to that provided by usual care (estimated by placebo arms)?	0	15
Given currently available evidence, in patients who have DI-CKD, is the evidence adequate to distinguish the net health benefit between roxadustat and ESAs?	0	15
Given currently available evidence, in patients who have DD-CKD, is the evidence adequate to distinguish the net health benefit between roxadustat and ESAs?	0	15

The CTAF Panel voted unanimously on all three comparative clinical effectiveness questions, judging the evidence inadequate across all treatments and comparisons. The substantial uncertainty surrounding mortality in all trials was a key driver of the votes.

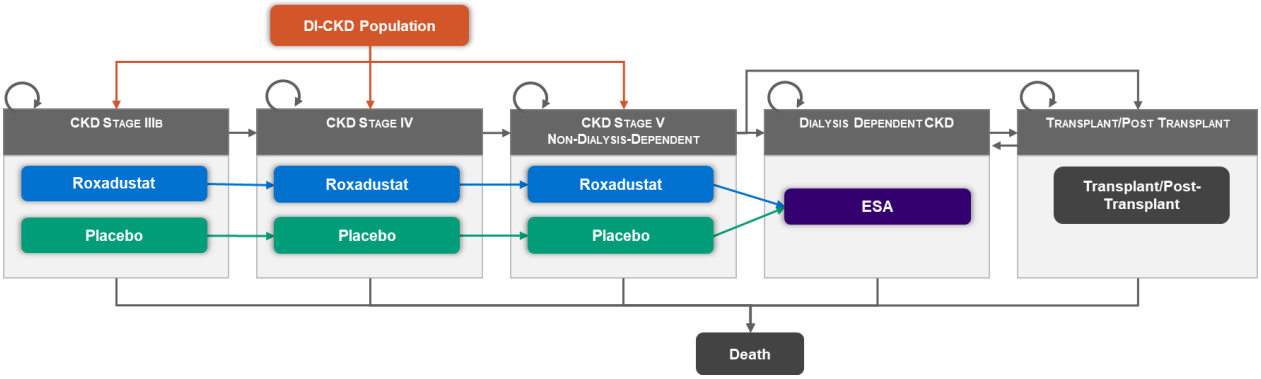
4. Long-Term Cost-Effectiveness

4.1. Methods Overview

The primary aim of this analysis was to estimate the cost effectiveness of roxadustat compared with ESAs for the treatment of anemia in patients with DI-CKD and in patients with DD-CKD using a decision analytic model. The base-case analysis took a health care system perspective focusing on direct medical care costs only with a lifetime time horizon and cycle length of four weeks. Because of the unique payment system under Medicare where ESAs are included in a bundled payment system, we considered co-base cases of a commercial payer perspective and Medicare perspective in the DD-CKD population. Costs and outcomes were discounted at 3% per year.

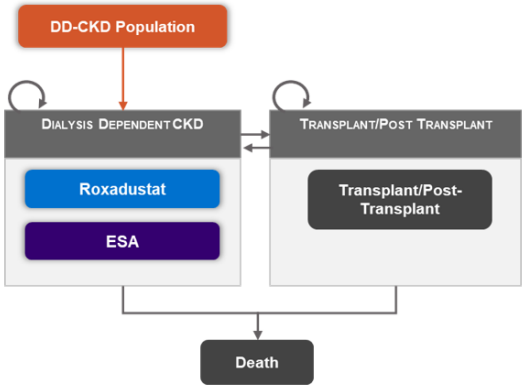
The model considered drug costs, administration costs, use of IV iron, serious adverse events, RBC transfusions, and MACE+. A modified societal perspective was undertaken as a scenario analysis, which included indirect costs due to lost productivity.

Figure 4.1. Model Structure, DI-CKD



CKD: chronic kidney disease, DI: dialysis-independent, ESA: erythropoiesis-stimulating agent

Figure 4.2. Model Structure, DD-CKD



CKD: chronic kidney disease, DD: dialysis-dependent, ESA: erythropoiesis-stimulating agent

DI-CKD stages IIIb, IV, V, DD-CKD, and transplant/post-transplant health states form the backbone of the model structure. Each CKD stage had a baseline Hb, utility, and costs. The DI-CKD population entered the model in CKD stages IIIb, IV, and V. The DD-CKD population entered the model in the DD-CKD stage. Overlaid upon this backbone were the outcomes of anemia, anemia treatment, adverse events, and MACE+. Clinical efficacy of anemia treatments was applied through a mean CFB Hb, representing an average across each cohort. In addition to the average, we also considered the proportion of patients with Hb <10.0 g/dL versus ≥10 g/dL.

Patients remained in the model until death. All patients could transition to death from all causes from any of the alive health states.

4.2. Key Model Assumptions and Inputs

Below is a list of key model choices:

- Lifetime time horizon
- Cycle length of four weeks
- Progression of underlying CKD based on published transition probabilities with no direct impact of anemia treatment on CKD progression
- 3% discount per year for costs and outcomes
- No discontinuation of roxadustat or ESAs considered
- DI-CKD patients will switch to ESAs upon progression to DD-CKD
- No impact on mortality or MACE+ events modeled in the DI-CKD population in the base case.

Our model includes several assumptions stated below (Table 4.1).

Table 4.1. Key Model Assumptions

Assumption	Rationale
No direct impact of anemia treatment on CKD progression.	There are limited data demonstrating a causal link between improving anemia and reduced risk of progression.
Equivalent efficacy and safety across ESAs.	Prior meta-analysis showed similar efficacy across ESAs.[60]
DI-CKD patients use subcutaneously administered forms of ESAs.	Due to improved convenience over IV-infused products, patients not receiving hemodialysis will choose a subcutaneously administered ESA.
All patients were assumed to switch to ESAs upon progression to DD-CKD.	This assumption isolates the effect of roxadustat in the DI-CKD population.
All patients will remain on roxadustat or ESAs (except upon progression to DD-CKD in the DI-CKD population analysis as noted above).	Although there was discontinuation from the clinical trials, it is assumed that all patients will continue to require and receive anemia management in the real world. To maintain the focus on the cost effectiveness of roxadustat, we have chosen not to allow patients to switch to ESAs in the roxadustat arm and assume that patients remain on ESAs in the ESA arm.

CKD: chronic kidney disease, DD: dialysis-dependent, DI: dialysis-independent, ESA: erythropoiesis-stimulating agent, IV: intravenous

Transition Probabilities

The underlying transitions between CKD stages and death were based on prior published models of CKD, data from the US Renal Data System Annual Report, or for death in DD-CKD, the pooled roxadustat Phase III trials. The same set of transition probabilities among CKD states was assigned to both roxadustat and ESAs.

Health State Utilities

Health state utilities were derived from publicly available literature (Table 4.2). For DI-CKD, utility values were taken from a survey of community-dwelling adults in England with various stages of DI-CKD, including none, and based on EuroQol EQ-5D-3L index scores. Utility scores for DD-CKD were based on EuroQol EQ-5D index scores for 192 patients undergoing dialysis in Canada. Utility increase post-transplant was derived using time tradeoff techniques in a study of 168 Canadian patients who underwent transplant. Finally, utility loss per 1 g/dL decrease in utility was taken from a study of patients with CKD stages III, IV, and IV that assessed correlation of HRQoL as measured by the Kidney Disease Quality of Life questionnaire with Hb levels. Subsequent published work that mapped these values were later mapped to utility values. We used consistent health state utility values across treatments evaluated in the model. The direct effect of anemia on quality of life was captured by the average quality-of-life decrement per 1 g/dl decrease in Hb level from a baseline of 13 g/dl from Finkelstein et al.[61] The baseline non-anemic health state utility values were adjusted

downward to account for the reduced quality of life of anemia using the baseline Hb values of the roxadustat clinical trials and utility loss per 1 g/dL decrease in Hb.[61] From there, the CFB for each treatment option was used to model an increase in utility values resulting from anemia treatment.

Table 4.2. Health State Utilities

Parameter	Value (95% CI)	Source; Method
Baseline DI-CKD Stage III without Anemia	0.82	Nguyen 2018; EQ-5D[62]
Baseline DI-CKD Stage IV/V without Anemia	0.72	Nguyen 2018; EQ-5D[62]
Baseline DD-CKD ESRD without Anemia	0.609 (0.566, 0.652)	Manns 2003; EQ-5D[63]
Utility Increase Post Transplant	0.13	Laupacis 1996; TTO[64]
Utility Loss per 1 g/dl Decrease in Hb (Reference Hb ≥13 g/dL)	0.0114	Finkelstein 2009;[61] SF-36 & mapping function from Ara 2008[65] as cited in Yarnoff 2016[66]

CI: confidence interval, CKD: chronic kidney disease, DD: dialysis-dependent, DI: dialysis-independent, ESRD: end-stage renal disease, g/dL: grams per deciliter, TTO: time tradeoff

MACE+

In the DI-CKD population, no statistically significant difference in risk of MACE or MACE+ events was found for roxadustat versus darbepoetin alpha in the head-to-head, open-label non-inferiority study (DOLOMITES).[17,67] Therefore, an equal rate of MACE events was applied for both roxadustat and ESAs for the DI-CKD population in the base case. We investigated the possibility of a reduction in MACE+ events as a scenario in the DI-CKD population (see Report Supplement Table E22 and Table E23 for MACE+ in the DI-CKD population scenario).

For the DD-CKD population, a statistically significant increase in time to MACE+ events (but not MACE events alone) was observed in the roxadustat arms compared with ESAs in the pooled analysis of HIMALAYAS, ROCKIES, and SIERRAS.[17] For this analysis, a constant per-cycle risk of each individual MACE+ event was applied to the ESA arm and then a relative effect of roxadustat for each MACE+ event was calculated based on a pooled analysis of all four Phase III trials of HIMALAYAS, ROCKIES, PYRENEES, and SIERRAS (all-cause mortality), or from the pooled analysis of HIMALAYAS, ROCKIES, and SIERRAs (MI, stroke, hospitalization for unstable angina, and congestive heart failure hospitalization). Individual MACE+ events rates for PYRENEES other than all-cause mortality were unavailable at the time of this report. Due to the uncertainty in these estimates, we also investigated the possibility of no reduction in MACE+ events as a scenario in the DD-CKD population.

Table 4.3. Occurrence of MACE+ Events by Treatment Arm in the DD-CKD Population over 52 Weeks in HIMALAYAS, ROCKIES, SIERRAS

	Roxadustat	ESA	RR or HR (95% CI)	Source
All-Cause Mortality	15.7%	15.4%	1.05 (0.88, 1.26)	ICER meta-analysis
MI	5.3%	5.6%	0.95 (0.73, 1.23)	[17]
Stroke	2.3%	2.6%	0.90 (0.60, 1.34)	[17]
Unstable Angina	0.9%	1.1%	0.82 (0.44, 1.52)	[17]
CHF Hospitalization	6.2%	8.6%	0.72 (0.58, 0.91)	[17,68]

CHF: congestive heart failure, CI: confidence interval, CKD: chronic kidney disease, DD: dialysis-dependent, ESA: erythropoiesis-stimulating agent, HR: hazard ratio, ICER: Institute for Clinical and Economic Review, MI: myocardial infarction, RR: risk ratio

MACE+ events were associated with a cost and reduction in utility for the cycle in which the event occurred and for subsequent post-event cycles for stroke and MI (see Report Supplement Table E11 and Table E12). Costs and utility tolls were additive for patients who experienced more than one MACE+ event.

Costs

Costs included the cost of drug, administration, IV iron, RBC transfusions, CKD stage, and MACE+. Full details of costs can be found in Section E2 of the Report Supplement. As roxadustat is not yet available, a placeholder price of net price of $6,500 per year was included based on pricing projections heard from analysts. Details for individual inputs that are outlined below can be found in Section E2 of the Report Supplement.

For the commercial perspective in the DI-CKD population, all ESAs were priced based on wholesale acquisition cost (WAC), with a net price calculated based on discounts obtained from SSR Health. For Mircera (methoxy polyethylene glycol epoetin beta), where no net pricing information was available, the average discount was assumed across ESAs, but excluding biosimilars. The price of ESAs was taken as a weighted average cost based on market share in the DI-CKD population. It was assumed that all DI-CKD patients use subcutaneously administered forms of ESAs. For the commercial perspective in the DD-CKD population, ESAs were priced at average sales price (ASP) plus 9.5% assuming an IV administration.

From the Medicare perspective considering a bundled payment system, all ESAs, IV iron, and RBC transfusions were assumed to be included in a fixed cost per cycle. Roxadustat was modeled as an additional add-on cost for three years, after which it was included in the bundle at no extra cost as is expected based on previous drugs covered via the Transitional Drug Add-on Payment Adjustment (TDAPA) process (e.g., Parsabiv® [etelcalcetide]).[69]

4.3. Results

Base-Case Results

DI-CKD Population, Commercial Perspective

Table 4.4 presents the results for the base-case analysis of roxadustat versus ESAs in the DI-CKD population from a commercial perspective. In the base case, no difference between roxadustat and ESAs was assumed for the proportion of patients with Hb level ≥10 g/dL, RBC infusions, or MACE+. As there were negligible differences in quality-adjusted life years (QALYs) and equal value life years (evLYs) and no difference in life years (LYs) with roxadustat, the resulting incremental cost-effectiveness ratio findings versus ESAs were not reported, and instead, incremental costs and incremental outcomes were report separately. Roxadustat was found to be cost-saving in this population due to the lower assumed cost of roxadustat versus ESAs and lower use of IV iron. The model resulted in a point estimate of $8,000 in lifetime cost savings with roxadustat, which remained likely cost-saving in probabilistic sensitivity analysis (-$9,000; 95% CrI -$13,000, -$5,000).

Table 4.4. Results for the Base Case for Roxadustat Compared to ESAs: DI-CKD, Commercial

Treatment	Drug Cost	IV Iron	RBC Transfusion	Other Costs*	Total Cost	QALYs	Life Years	evLYs
ESAs	$52,000	$1,090	$274	$362,000	$416,000	5.21	7.40	5.21
Roxadustat	$44,000	$987	$274	$362,000	$408,000	5.21	7.40	5.21
Incremental†	-$8,000	-$103	$0	$0	-$8,000	<0.01	0.00	<0.01

ESA: erythropoiesis-stimulating agent, evLY: equal-value life year, IV: intravenous, QALY: quality-adjusted life year, RBC: red blood cell

*Includes adverse events, MACE+, and cost of CKD health states.

†Rounding within treatment-specific findings may produce differences when compared to the incremental findings.

DD-CKD Population, Commercial Perspective

Table 4.5 and Table 4.6 list the results for the base-case analysis of roxadustat versus ESAs in the DD-CKD population from a commercial perspective. Fewer LYs and QALYs were gained with roxadustat due to the point estimate for all-cause mortality demonstrating increased mortality. Roxadustat resulted in a lower total cost based on the assumed placeholder price for roxadustat, fewer RBC transfusions, and point estimates for reduction in MACE+. There was considerable uncertainty around this incremental total cost point estimate, as illustrated by the results of probabilistic sensitivity analysis, which yielded a credible range of -$329,000 to $316,000.

Table 4.5. Results for the Base Case for Roxadustat Compared to ESAs: DD-CKD, Commercial

Treatment	Drug Cost	IV Iron	RBC Transfusion	Other Costs*	Total Cost	QALYs	Life Years	evLYs
ESAs	$28,000	$4,588	$347	$775,000	$808,000	3.72	6.16	3.72
Roxadustat	$29,000	$4,390	$277	$745,000	$779,000	3.64	6.00	3.64
Incremental†	$1,000	-$285	-$70	-$30,000	-$29,000	-0.08	-0.17	-0.08

ESA: erythropoiesis-stimulating agent, evLY: equal-value life year, IV: intravenous, QALY: quality-adjusted life year, RBC: red blood cell

*Includes adverse events, MACE+, and cost of CKD health states.

†Rounding within treatment-specific findings may produce differences when compared to the incremental findings.

Table 4.6. Additional Results for the Base Case for Roxadustat Compared to ESAs: DD-CKD, Commercial

Treatment	LY Hb≥ 10 g/dL	RBC Transfusions	Strokes	MIs	Angina Hospitalizations	CHF Hospitalizations
ESAs	2.67	0.59	0.10	0.22	0.04	0.35
Roxadustat	3.63	0.47	0.09	0.21	0.04	0.33
Incremental*	0.96	-0.12	-0.01	-0.01	-0.01	-0.02

CHF: congestive heart failure, ESA: erythropoiesis-stimulating agent, LY: life year, MI: myocardial infarction, RBC: red blood cell

*Rounding within treatment-specific findings may produce differences when compared to the incremental findings.

DD-CKD Population, Medicare Perspective

Costs for the Medicare perspective are presented on the following page in Table 4.7. Outcomes were identical to the commercial perspective in Tables 4.5 and 4.6 above. As with the commercial perspective, fewer LYs and QALYs were gained with roxadustat at a lower cost based on the assumed placeholder price for roxadustat, fewer RBC transfusions, and point estimates for reduction in MACE+. Also similar to the commercial perspective, probabilistic sensitivity analysis yielded a credible range of cost saving (-$368,000) to cost increasing ($329,000). Although the three years of roxadustat outside the bundle at a cost of $6,500 per year is assumed, the full cost result is less than $19,500 ($6,500*3), primarily attributable to the high mortality rate among patients with DD-CKD.

Table 4.7. Results for the Base Case for Roxadustat Compared to ESAs: DD-CKD, Medicare

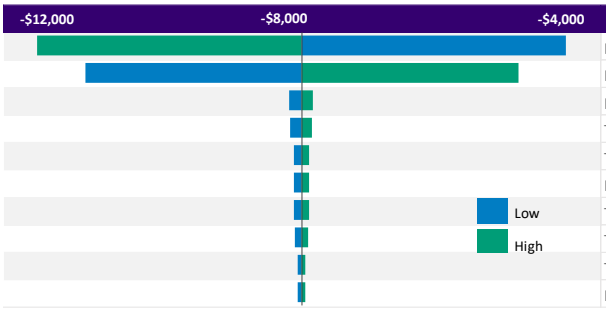
Treatment	Drug Cost	IV Iron	RBC Transfusion	Other Costs†	Total Cost
ESAs	$0*	$0	$0	$948,000	$948,000
Roxadustat	$14,000	$0	$0	$913,000	$927,000
Incremental‡	$14,000	$0	$0	-$34,000	-$21,000

ESA: erythropoiesis-stimulating agent, IV: intravenous, RBC: red blood cell
*Included in bundled payment as part of total cost of care.
†Includes adverse events, MACE+, and cost of Medicare bundled payment.
‡Rounding within treatment-specific findings may produce differences when compared to the incremental findings.

Sensitivity Analyses

One-way sensitivity analyses (OWSAs) were conducted for the outcome of total incremental cost in each population. In the DI-CKD population (Figure 4.2), the cost of roxadustat was by far the most impactful parameter on total incremental cost versus ESAs. In the DD-CKD population (Figure 4.3), the impact on all-cause mortality, stroke, and MI were the most impactful parameters, followed by the cost of roxadustat and ESAs.

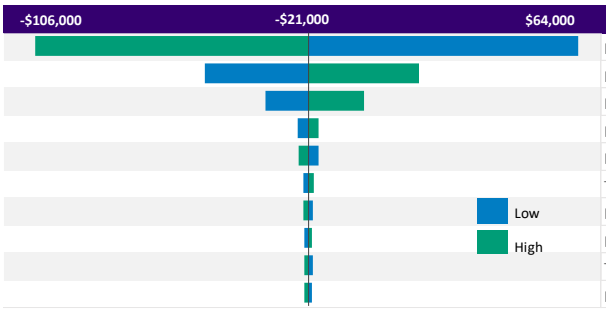
Figure 4.2. Tornado Diagram: DI-CKD, Commercial, OWSA of Incremental Cost



Parameter	Base Case	Low Value	High Value
Direct cost of ESAs, DI-CKD	$609.42	$548.48	$670.37
Direct cost of roxadustat, DI-CKD	$498.71	$448.84	$548.59
HR for mortality post-stoke & MI, DI-CKD	4.15	3.30	5.23
Transition probability Stage IV to death	0.080	0.072	0.1
Transition probability Stage IIIb to death	0.041	0.037	0.0
Discount rate for costs	0.23%	0.21%	0.0
Transition probability Stage IIIb to IV	0.137	0.123	0.2
Transition probability Stage IV to Stage V	0.081	0.073	0.1
Transition probability Stage V to DD-CKD	0.626	0.563	0.7
Risk of MI, ESAs, DI-CKD	0.27%	0.2%	0.3%

DD-CKD: dialysis-dependent chronic kidney disease, DI-CKD: dialysis-independent chronic kidney disease, ESA: erythropoiesis-stimulating agent, HR: hazard ratio, MI: myocardial infarction

Figure 4.3. Tornado Diagram: DD-CKD, Commercial, OWSA of Incremental Cost



Parameter	Base Case	Low Value	High Value
RR for all-cause mortality vs ESAs, DD-CKD	1.05	0.88	1.26
RR for MI vs ESAs, DD-CKD	0.95	0.73	1.23
RR for stroke vs ESAs, DD-CKD	0.90	0.60	1.34
Direct cost of roxadustat, DD-CKD	$498.71	$448.84	$548.59
Direct cost of ESAs, DD-CKD	$465.59	$419.04	$512.15
Transition probability DD-CKD to death	0.154	0.138	0.2
Direct cost of transplant event	$19,636	$17,672	$21,600
Discount rate for costs	0.23%	0.21%	0.0
Transition probability DD-CKD to transplant	0.035	0.032	0.0
Direct cost of DD-CKD	$6,902	$6,212	$7,592

DD-CKD: dialysis-dependent chronic kidney disease, ESA: erythropoiesis-stimulating agent, evLY: equal-value life year, LY: life year, MI: myocardial infarction, RR: risk ratio

Scenario Analyses

Results for key scenarios for the DI-CKD population are presented in Table 4.8. For the base-case analysis and modified societal perspective, roxadustat was associated with cost savings with similar health benefits to ESAs (i.e., health benefits in between 0 and 0.01). If a potential impact on MACE+ was considered versus ESAs based on the point estimates for relative risk of individual MACE+ in the DOLOMITES trial, roxadustat resulted in 0.48 more QALYs at a higher cost ($27,000) compared with ESAs. When considering the uncertainty around the point estimates for all-cause mortality in DOLOMITES (HR: 0.85, 95% CI: 0.52, 1.37), the resulting incremental QALYs could range from 1.11 additional QALYs gained using the lower bound of the 95% CI to 0.35 fewer QALYs gained using the upper bound of the 95% CI.

Table 4.8. Scenario Analysis Results: DI-CKD, Commercial

Roxadustat vs. ESAs	Base-Case Results	Modified Societal	Impact on MACE+
Incremental Cost	-$8,000	-$9,000	$27,000
Incremental QALYs	<0.01	<0.01	0.48

ESA: erythropoiesis-stimulating agent, MACE: major adverse cardiovascular event, QALY: quality-adjusted life year

Results for key scenarios for the DD-CKD population are presented in Table 4.9. For all scenarios evaluated and consistent with the base-case results, the incremental cost per QALY for roxadustat versus ESAs were not presented.

Table 4.9. Scenario Analysis Results: DD-CKD

Treatment	Base-Case Results	Modified Societal	No Impact on MACE+
Roxadustat vs. ESAs, Commercial Perspective			
Incremental Cost	-$29,000	-$28,000	$1,500
Incremental QALYs	-0.08	-0.08	0.01
Roxadustat vs. ESAs, Medicare Perspective			
Incremental Cost	-$21,000	-$20,000	$14,000
Incremental QALYs	-0.08	-0.09	0.01

ESA: erythropoiesis-stimulating agent, MACE: major adverse cardiovascular event, QALY: quality-adjusted life year

Additional details for these scenarios can be found in the Report Supplement Section E5 and Section E6.

Total Health Care Cost Neutrality Analyses

For the base-case analysis in the DI-CKD population, there was no difference in QALYs between roxadustat and ESAs. For the DD-CKD population in the base case, fewer QALYs were generated with roxadustat. For the purposes of considering threshold analyses concepts, we opted to assume the scenario within the DD-CKD population of no differences in MACE+ (and no differences in all-cause mortality). Given only negligible differences in long-term health outcomes such as the incremental QALY for the DI-CKD base case as well as the scenario within the DD-CKD population

that assumed no differences in MACE+, threshold prices approximate analyses that estimate the roxadustat annual treatment cost that would achieve total health care cost neutrality when compared to the ESA treatment alternative. In the DI-CKD population, the annual cost of roxadustat that would be total health care cost neutral was $7,962 per year. In the DD-CKD population from the commercial perspective where we assumed no differences in MACE+ (and no difference in all-cause mortality), the annual cost of roxadustat that would be total health care cost neutral was $6,184 per year. In the DD-CKD population from the Medicare perspective where we assumed no differences in MACE+ (and no difference in all-cause mortality), the annual cost of roxadustat that would be total health care cost neutral was $139 per year.

Model Validation

Model validation is described in Section E7 of the Report Supplement.

Uncertainty and Controversies

CFB in Hb was included to capture the impact of anemia on quality of life, but both roxadustat and ESAs are capable of increasing Hb and this was not a model driver. The QALYs gained (or lost) in our economic model are driven by the relative effect of roxadustat on all-cause mortality and MACE.

Although we have attempted to take a comprehensive approach to capture relevant costs and outcomes related to CKD and anemia, our model does not account for all possible short-term and long-term negative consequences of RBC transfusions, such as increased risk of kidney transplant rejection.

In the DI-CKD population, only one study provides evidence for roxadustat versus darbepoetin alfa, and it shows a numerical reduction in all-cause mortality and MACE+. However, the difference is not statistically significant, with wide confidence intervals. Additional data are needed to confirm these findings.

In the DD-CKD population, the pooled analysis of three Phase III studies demonstrated a statistically significant reduction in MACE+ events (which includes all-cause mortality) and the point estimates for all-cause mortality and the relative risk of each MACE+ event favored roxadustat, while only statistically significant for congestive heart failure hospitalizations. Considerable uncertainty exists in these estimates. When all-cause mortality for the fourth Phase III study (PYRENEES) was pooled, all-cause mortality favored ESAs. No information was available at the time of this report on the rate of other individual MACE+ events in PYRENEES, so we were unable to conduct an analysis using the relative risk of MACE+ events using the totality of evidence. When any impact on MACE+ was removed from the economic analysis, roxadustat was no longer cost-saving, as all patients experienced equal all-cause mortality and MACE+, but was close to cost neutral, and resulted in a small QALY gain due to greater improvement in Hb.

4.4 Summary and Comment

The results of our economic analysis show that roxadustat may be cost saving in the DI-CKD population with similar or improved health benefit, using the placeholder price of roxadustat of $6,500 per year, but with a high degree of uncertainty.

In the DD-CKD population, roxadustat may be cost-saving (depending on the actual net price) with the potential for less health benefit, driven by the uncertainty in relative all-cause mortality compared with ESAs.

Altogether, we generally observed cost-savings if roxadustat was priced at the placeholder price of $6,500 per year, approximately price-parity with ESAs from a commercial payer perspective, but with a high degree of uncertainty. When we removed MACE+ from the analysis in the DD-CKD population, the results suggest higher costs from the Medicare perspective, assuming roxadustat was reimbursed outside the bundled payment for three years.

5. Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that was not available in the evidence base nor could be adequately estimated within the cost-effectiveness model. These elements are listed in the table below, with related information gathered from patients and other stakeholders. Following the public deliberation on this report the appraisal committee will vote on the degree to which each of these factors should affect overall judgments of long-term value for money of the intervention in this review.

Table 5.1. Categories of Potential Other Benefit and Contextual Considerations

Potential Other Benefit or Contextual Consideration	Relevant Information
Assumptions made in the base-case cost-effectiveness estimates rendering results overly optimistic or pessimistic.	N/A
Whether the intervention represents a similar or novel mechanism of action compared to that of other active treatments.	HIF-PH inhibitors offer a novel mechanism of action to treat anemia that is different from ESAs. There will likely be patients who get benefit from roxadustat who could not be adequately managed with ESAs.
Whether the delivery mechanism or relative complexity of the intervention under review is likely to have very different real-world outcomes relative to an active comparator than estimated from clinical trials.	In patients with DD-CKD, an oral medication may have decreased adherence compared to an infusion administered with dialysis, but potentially greater adherence than a home-administered subcutaneous injection. In patients with DI-CKD, an oral medication may have increased adherence compared to an injection form especially for patients who are unable to receive these injections at home. As such, relative adherence and complexity will likely vary by patient group.
Whether the intervention could reduce or preclude the potential effectiveness of future treatments.	N/A
Whether the intervention offers a special advantage for some patients by virtue of presenting an option with a notably different balance or timing of risks and benefits.	N/A
Whether the intervention differentially benefits a historically disadvantaged or underserved community.	The prevalence of CKD is higher in the African American community in the US than in the white population.
Whether there is a notably large or small health loss without this treatment as measured by absolute QALY shortfall.	The absolute QALY shortfall in the DI-CKD population assuming treatment with ESAs was 19.23 (from 25.75 QALYs in the general population to 6.52 in the DI-CKD population). The absolute QALY shortfall in the DD-CKD population assuming treatment with ESAs was 20.86 (from 25.75 QALYs in the general population to 4.89 in

Potential Other Benefit or Contextual Consideration	Relevant Information
	the DD-CKD population). See the Report Supplement for further details.
Whether there is a notably large or small health loss without this treatment as measured by proportional QALY shortfall.	The proportional QALY shortfall in the DI-CKD population assuming treatment with ESAs was 75%. The proportional QALY shortfall in the DD-CKD population assuming treatment with ESAs was 81%. See the Report Supplement for further details.
Whether the intervention will significantly reduce the negative impact of the condition on family and caregivers versus the comparator.	The availability of an oral option will decrease the need for frequent visits to receive ESAs for patients who cannot receive these at home. This could decrease caregiver burden.
Whether the intervention will have a significant impact on improving return to work and/or overall productivity versus the comparator.	The availability of an oral option will decrease the need for frequent visits to receive ESAs for patients who cannot receive these at home. This could reduce time away from work.

DD-CKD: dialysis-dependent chronic kidney disease, DI-CKD: dialysis-independent chronic kidney disease, ESA: erythropoiesis-stimulating agent, HIF-PH: hypoxia-inducible factor-prolyl hydroxylase, N/A: not applicable, QALY: quality-adjusted life year

CTAF Votes

At the Public Meeting, CTAF deliberated and voted on the relevance of specific potential other benefits and contextual considerations on judgments of value for the interventions under review. The results of the voting are shown below. Further details on the intent of these votes to help provide a comprehensive view on long-term value for money are provided in the ICER Value Assessment Framework.

Please vote 1, 2, or 3 on the following potential other benefits and contextual considerations; for questions where a comparator or existing therapy is implied, please answer for roxadustat compared to ESAs:

1 (Suggests Lower Value)	2 (Neutral)	3 (Suggests Higher Value)
DI-CKD: Uncertainty or overly favorable model assumptions creates significant risk that base-case cost-effectiveness estimates are too optimistic.		**DI-CKD:** Uncertainty or overly unfavorable model assumptions creates significant risk that base-case cost-effectiveness estimates are too pessimistic.
2 votes	***13 votes***	0 votes

A majority of the Panel voted that the model assumptions for the DI-CKD population were neither overly favorable nor unfavorable for roxadustat. The Panel based their vote on the high levels of uncertainty in the model.

1 (Suggests Lower Value)	2 (Neutral)	3 (Suggests Higher Value)
DD-CKD: Uncertainty or overly favorable model assumptions creates significant risk that base-case cost-effectiveness estimates are too optimistic.		**DD-CKD:** Uncertainty or overly unfavorable model assumptions creates significant risk that base-case cost-effectiveness estimates are too pessimistic.
1 vote	***14 votes***	0 votes

A majority of the Panel voted that the model assumptions for roxadustat in the DD-CKD population were neither overly favorable nor unfavorable given the considerable uncertainty in the model.

1 (Suggests Lower Value)	2 (Neutral)	3 (Suggests Higher Value)
Very similar mechanism of action to that of other active treatments.		New mechanism of action compared to that of other active treatments.
0 votes	1 vote	***14 votes***

A majority of the Panel voted that roxadustat represents a new mechanism of action compared to existing treatments (i.e., ESAs). Roxadustat is an oral HIF-PH inhibitor that mimics the response to hypoxia.

1 (Suggests Lower Value)	2 (Neutral)	3 (Suggests Higher Value)
Delivery mechanism or relative complexity of regimen likely to lead to much lower real-world adherence and worse outcomes relative to an active comparator than estimated from clinical trials.		Delivery mechanism or relative simplicity of regimen likely to result in much higher real-world adherence and better outcomes relative to an active comparator than estimated from clinical trials.
0 votes	6 votes	***9 votes***

A majority of the Panel voted that the relative simplicity of the treatment regimen for roxadustat is likely to result in much higher real-world adherence and better outcomes relative to other treatment options. That being said, it was noted that relative adherence and complexity may vary by patient population (i.e., in patients with DD-CKD, an oral medication may not have increased adherence compared to an infusion administered with dialysis, but potentially greater adherence than a home-administered subcutaneous injection).

1 (Suggests Lower Value)	2 (Neutral)	3 (Suggests Higher Value)
This intervention will not differentially benefit a historically disadvantaged or underserved community.		This intervention will differentially benefit a historically disadvantaged or underserved community.
5 votes	***6 votes***	4 votes

A slight majority of the Panel judged that roxadustat would have a "neutral" impact on historically disadvantaged or underserved communities. Panelists who suggested that roxadustat may benefit these populations noted that the prevalence of CKD is higher among Black and African Americans, and the availability of an oral option may benefit patients in rural areas where dialysis centers are sparse and among patients who may have a limited ability to take time away from work/school and/or travel to dialysis facilities to receive treatment.

1 (Suggests Lower Value)	2 (Neutral)	3 (Suggests Higher Value)
Small health loss without this treatment as measured by absolute QALY shortfall.		Substantial health loss without this treatment as measured by absolute QALY shortfall.
0 votes	5 votes	***10 votes***
Small health loss without this treatment as measured by proportional QALY shortfall.		Substantial health loss without this treatment as measured by proportional QALY shortfall.
0 votes	6 votes	***9 votes***

A majority of the Panel voted that substantial health loss would occur without treatment for patients with CKD as calculations for both the DI-CKD and DD-CKD populations demonstrated a loss of 75-81% of total quality-adjusted life expectancy relative to individuals without CKD. CKD represents an illness with a high lifetime burden with serious lifelong effects on quality of life.

1 (Suggests Lower Value)	2 (Neutral)	3 (Suggests Higher Value)
Will not significantly reduce the negative impact of the condition on family and caregivers vs. the comparator.		Will significantly reduce the negative impact of the condition on family and caregivers vs. the comparator.
2 votes	***7 votes***	6 votes

The Panel was nearly split on whether roxadustat would reduce the impact of CKD on family/caregivers or have a neutral effect. It was noted by some that the availability of an oral option may potentially decrease the need for frequent visits to receive ESAs, which in turn could decrease caregiver and family burden substantially.

1 (Suggests Lower Value)	2 (Neutral)	3 (Suggests Higher Value)
Will not have a significant impact on improving return to work and/or overall productivity vs. the comparator.		Will have a significant impact on improving return to work and/or overall productivity vs. the comparator.
3 votes	***8 votes***	4 votes

A majority of the Panel voted that the impact of roxadustat on productivity would be neutral. Though the availability of an oral option may decrease the need for frequent visits to receive ESAs for some patients, for others, visits to dialysis may still be necessary due to their treatment regimen.

6. Health Benefit Price Benchmarks

Health benefit price benchmarks (HBPBs) for the annual cost of treatment with roxadustat were not presented within this report given the "insufficient" evidence ratings in the DI and DD populations when comparing roxadustat to ESAs and based on the decision to present the incremental outcomes and incremental costs rather than as incremental cost-effectiveness ratios.

CTAF Vote

No value votes were taken at the Public Meeting. As described in ICER's Value Assessment Framework, questions on long-term value for money are subject to a value vote only when an established net price is available or if net price estimates are felt to be extremely reliable.

7. Potential Budget Impact

7.1. Overview of Key Assumptions

The aim of the potential budgetary impact analysis is to document the percentage of patients who could be treated at selected prices without crossing a potential budget impact threshold that is aligned with overall growth in the US economy. For 2019-2020, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to be approximately $819 million per year for new drugs.

We used results from the cost-effectiveness model to estimate the potential total budgetary impact of anemia treatments such as roxadustat in patients with DI-CKD and in patients with DD-CKD. We used epidemiology evidence to estimate the US population with anemia for CKD stages III through V. We note that given the safety profile of currently available treatments including ESAs, the population that is currently taking ESAs and may consider roxadustat, if available, is a subset of those with anemia and CKD. To account for this difference between an anemia with CKD population and the subset currently taking ESAs, we assumed 50% of those who self-reported as having anemia treatment were taking ESAs and may be eligible for roxadustat. Other approaches to estimate the number of patients taking ESAs for CKD include following Kidney Disease Improving Global Outcomes recommendations and may lead to lower estimates of a roxadustat eligible population when comparing to those currently taking ESAs. Given the emerging safety evidence for roxadustat, we first characterized the broader population approach of anemia for CKD stages III through V. This characterization allows for the flexibility of evaluating future treatments of anemia for CKD with varying safety profiles.

We assumed a commercial payer perspective for the DI-CKD population and a Medicare payer perspective where ESAs are included in a bundled payment system for the DD-CKD population. Note that the price of roxadustat remains unknown and a placeholder price of $6,500 per year was assumed. To estimate the roxadustat eligible population in DI-CKD and DD-CKD, we referenced the following US epidemiological evidence:

- US CKD prevalence is approximately 37 million[70,71]
    - 42.9% are stage III; 2.5% are stage IV; 0.9% are stage V[71]
    - Anemia prevalence by stage is: 17.4% for stage III; 50.4% for stage IV; 53.4% for stage V[4]; and of those with anemia, self-reported anemia treatment by stage is: 26.5% for stage III; 20.7% for stage IV; 43.0% for stage V[4]

Assuming the DD-CKD population was approximately equal to stage V and assuming that 50% of those who self-reported as having anemia treatment were taking ESAs and therefore eligible for

roxadustat, we estimated an annual N=414,204 DI-CKD patients and N=38,232 DD-CKD patients eligible to potentially take roxadustat.

7.2. Results

Assuming a placeholder annual price of $6,500 per year for roxadustat and assuming only 8.45% of the treated population was DD-CKD and therefore from the Medicare payer perspective, the average annual costs per treated patient (roxadustat vs. ESAs) was -$799. The annualized potential budget impact over five years was -$220 million when treating the whole population over five years. Given the cost differences between the commercial payer perspective and the Medicare payer perspective, the budget impact turns positive when assuming a Medicare payer perspective for the DD-CKD population. For the DD-CKD population Medicare payer perspective, the average annual cost per treated patient (roxadustat vs. ESAs) was $3,270. The annualized potential budget impact over five years was $59 million when treating the whole subpopulation of eligible DD-CKD patients given the placeholder roxadustat price of $6,500 per year. The current placeholder pricing and assumptions do not approach the budget impact threshold.

8. Policy Recommendations

Following its deliberation on the evidence, CTAF engaged in a moderated discussion with a policy roundtable about how best to apply the evidence on the use of roxadustat. The policy roundtable members included two patient advocates, two clinical experts, two payers, and two representatives from drugmakers. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants.

The roundtable discussion was facilitated by Dr. Steven D. Pearson, MD, MSc, President of ICER. The main themes and recommendations from the discussion are organized by audience and summarized below.

All Stakeholders

All stakeholders have a responsibility and an important role to play in ensuring that effective new treatment options for patients with CKD are introduced in a way that will help reduce health inequities.

People from diverse racial and ethnic backgrounds are at a higher risk of developing CKD. Unfortunately, patients from these communities are also at a higher risk of not receiving adequate education on anemia or on treatment options for this condition. All stakeholders should accept and act upon their responsibility to address these disparities.

- ***Manufacturers should engage with people from diverse communities to help inform the design and implementation of clinical trials, ensure that patients enrolled in pivotal trials are fully representative of people of color and those from less advantaged backgrounds, and should commit to designing trials that capture the comprehensive set of patient outcomes that matter most to patients.***
- ***Payers should engage with people from diverse CKD patient groups and with clinical experts in order to infuse coverage policies with sensitivity to the way that different treatments may offer distinct advantages or disadvantages for people based on their social background and living situation.***
- ***Patient advocacy groups for people with CKD should seek to represent diverse perspectives, requiring outreach to patients who are often not engaged by academic health systems, manufacturers, or other policymakers. Patient groups should consider collaborating with organizations and people in diverse communities to help build the trust needed to empower all patients. Among other important goals, educational outreach about anemia is lacking for many patients and their families.***

- ***Clinicians should follow the principle of shared decision-making to ensure that the values of patients with diverse needs and perspectives on risks and benefits of different treatments are at the heart of all treatment decisions.***

Regulators

Given the level of uncertainty about the benefits versus harms and the long-term effect of using roxadustat compared to ESAs, we strongly suggest a mandate for a registry or other rapid and comprehensive post-marketing assessment.

At the time of this report, the FDA has not yet rendered a decision on regulatory approval for roxadustat. However, CTAF voted unanimously that the evidence was not currently adequate to demonstrate its superiority to usual care. The history of using ESAs to treat anemia in patients with CKD taught the medical community an important lesson about the risks of treating to blood test levels without fully understanding the true clinical outcomes for patients. Much harm was done until multiple RCTs emerged to show that correction of anemia and maintenance of Hb to near normal levels with ESAs increased mortality and cardiovascular events without consistently improving quality of life. Despite its clear ability to raise Hb levels, roxadustat lacks adequate evidence at this time to demonstrate convincingly that at doses and targets used in clinical trials, it does not have an adverse effect on mortality. Therefore, if roxadustat is approved by the FDA, the regulator should require a substantial post-marketing program of evidence generation to establish with more certainty the effects of treatment on mortality and cardiovascular outcomes.

Manufacturer

The manufacturer should not hold data in confidence from RCTs completed more than one to two years ago. The company has a responsibility to patients and clinicians to move these data into the public domain, to submit data rapidly for peer review in advance of regulatory approval, and to share these data in a transparent manner with groups seeking to assess the evidence to inform clinical practice and policy.

Several pivotal studies for roxadustat have been completed for over the past one to two years, yet the data have not all been submitted for peer reviewed publication. This by itself raises questions about the commitment of the manufacturer to transparency and suggests that the company may be trying to hold the data in-confidence in order to manage the narrative about results. Similarly, the practice followed by this manufacturer of reporting pooled data from different trials undermines the ability of clinicians, patients, and other stakeholders to perform an adequate analysis of the risks and benefits of treatment. The manufacturer should adopt the best practices of other companies in making clinical trial evidence more accessible in a timely fashion.

If roxadustat gains regulatory approval, the manufacturer should price the drug in alignment with its demonstrated value, which at the current time is highly uncertain given the lack of clarity about overall mortality and cardiovascular outcomes. In this setting, with significant uncertainty of this magnitude, the manufacturer should set the price lower than treatments with more established evidence and wait until further evidence addresses the uncertainties before seeking a higher price.

Manufacturer and Researchers

The manufacturer and researchers should avoid focusing primarily on Hb levels and the need for transfusion. Future research should expand outcomes measured to include patient-relevant outcomes such as quality of life, functional status, fatigue, overall cardiovascular events, and mortality in addition to the need for transfusion.

Researchers should conduct real-world comparative studies of roxadustat versus ESAs that evaluate a broad set of patient subgroups including ethnic and racially diverse populations and those who are hyporesponsive to ESAs.

Clinicians highlighted that using roxadustat would be of interest especially in the patients who are hyporesponsive to ESA, which is a group that has not been explicitly assessed in the current trials.

Clinicians

Clinicians should have decision support tools and invest the time needed for shared decision-making given the uncertainty and potential variability in patients' values about an oral treatment option for anemia in CKD.

We heard that an oral option will likely be more important for DI-CKD and home dialysis patients, especially for patients receiving peritoneal dialysis where an oral treatment could reduce the need for injections. We also learned that particularly for patients receiving in-center hemodialysis, an infused option included in dialysis is likely easier than taking an additional oral medication. Patients stressed the need to explore values among different groups including ethnic and racial minorities and that it will be beneficial to engage with representatives from these communities.

Given the mechanism of action for roxadustat, patients were excluded from clinical trials if they had acute coronary syndrome, acute stroke, acute seizure, or thrombotic event within the last 12 weeks. Until further data are gathered, clinicians should consider delaying treatment with roxadustat for patients with this clinical scenario.

Chronic anemia treatment in most patients is not an emergent situation. Postponing treatment with roxadustat should be considered in these patient subgroups to reduce the risk of harm.

Patient Organizations

Patients and advocacy groups should continue their efforts to encourage innovation while pushing manufacturers to generate better evidence to guide patient and clinician decision-making.

Patients have the most to gain from better evidence on the comparative safety and effectiveness of new treatments.

Patients and advocacy groups should emphasize the need for education and developing educational materials, which will facilitate shared decision making by summarizing potential benefits, harms, and evidence gaps about roxadustat compared to ESAs.

There is a need for an organized effort from educators, families, patients, advocacy groups, and clinicians to provide information about different treatment options in lay language that will facilitate shared decision-making. This effort should involve organizations on the ground, existing partnership with patients advocates, local faith-based organizations, and clinics. In order for shared decision-making to be feasible and effective, the knowledge gaps around anemia should be highlighted and dealt with. This is especially important for ethnic and racially diverse groups and for all underserved and vulnerable populations.

Payers

If approved by the FDA, roxadustat will present a novel mechanism of action and an oral treatment option for patients. There is no current evidence demonstrating that roxadustat is superior to ESAs. As a treatment that would be indicated for patients prior to ESRD and those with ESRD, the coverage and treatment issues will be very different for private payers as opposed to patients with Medicare.

Reimbursement Considerations for Private Payers (Primarily DI-CKD Patients)

Given the lack of evidence to differentiate the clinical effectiveness, private payers may consider whether their formularies require both roxadustat and one or more ESAs. However, the different delivery mechanism may have important advantages or disadvantages for different patients, suggesting that both options should be covered.

It is possible that private payers may consider negotiating lower prices with manufacturers of ESAs and roxadustat by offering not only preferred formulary tiering but exclusive formulary placement. The lack of robust evidence on the cardiovascular and overall mortality outcomes for roxadustat may also lead some private payers to consider not adding this treatment to their formulary. We heard from patient advocates and clinical experts that the distinctive oral delivery mechanism for roxadustat will create important potential benefits for some patients, whereas for others the ESAs

will remain a preferred option, suggesting that payers fully engage with all stakeholders if they wish to consider a narrow formulary.

Given the significant uncertainty that remains about the effectiveness of roxadustat, it is reasonable for payers to use prior authorization as a component of coverage.

Prior authorization criteria for roxadustat should be based on clinical evidence and input from clinical experts and patient groups. The process for authorization should be clear and efficient for providers. It is possible that the numbers of DI-CKD patients who could be started on roxadustat exceeds the current number on ESAs. Options for specific elements of coverage criteria within insurance coverage policy are discussed below.

Coverage Clinical Criteria Considerations:

A. ***Patient Eligibility Criteria***: The patient eligibility criteria are likely to mirror those in the clinical trials, which were very similar to existing coverage criteria for ESAs. One common set of criteria are: adult patients with DI-CKD (stages III-V) with an eGFR <60 ml/min/m^2 or adult patients with DD-CKD who have anemia with a Hb <10-10.5 g/dl. Some payers cover ESAs not for treatment of anemia-related symptoms such as fatigue, but only when the "therapeutic goal is reducing the risk of alloimmunization and/or other RBC transfusion related risks."[72] However, this therapeutic goal criteria would seem to be difficult to operationalize further and may not prove useful.

B. ***Exclusion Criteria***: Trials of roxadustat excluded patients with multiple conditions, which payers may consider when determining eligibility criteria for treatment. The exclusion criteria include:

    - Active infection
    - Known history of any of the following conditions: myelodysplastic syndrome or multiple myeloma, thalassemia, sickle cell anemia, pure red cell aplasia, hemochromatosis or coagulation disorder, gastrointestinal bleeding, chronic liver disease, NYHA Class III or IV congestive heart failure, MI, acute coronary syndrome, acute stroke, acute seizure, or recent thrombotic event (within the last 12 weeks), malignancy that has not been in remission for at least five years, HIV, hepatitis B or C, untreated proliferative diabetic retinopathy, diabetic macular edema, macular degeneration, or retinal vein occlusion
    - Prior organ transplant
    - Pregnant or breastfeeding

Step Therapy:

Given that the evidence is not adequate to distinguish clinical benefit and that there are more data and years of clinical experience with ESAs, some payers may wish to consider stepping through ESAs if they are substantially lower-priced than roxadustat before obtaining coverage for a more expensive option.

Given the uncertainty about the clinical benefits and harms and lack of long-term safety data, stepping through roxadustat first is not advisable, however, step therapy through ESAs may be an approach some payers will consider, especially if ESAs offer a lower overall cost of care. However, as noted earlier, patient advocates and clinical experts highlighted the potential distinctive living situations and other factors that might make an oral option not just preferred by the patient but the option that would have the best chance of achieving the intended clinical outcome. This situation might arise for patients who are house-bound or are challenged with transportation to clinics and infusion centers. Therefore, if step therapy is to be considered, rapid, transparent exception mechanisms should be in place.

Concomitant Use with ESAs:

All key clinical trials have allowed rescue therapy using ESAs in addition to roxadustat as part of the protocol. However, data on the safety and efficacy of concomitant use of these agents has not been presented.

Provider Qualifications:

Giving the tenuous risk and benefit tradeoffs and the need for close follow-up, payers may wish to require that management of roxadustat be done by or in consultation with a specialist.

Management of anemia in CKD is complex and requires regular follow up to adjust dosing of treatments and iron supplementation. One of the main concerns with roxadustat is the fact that high-risk patients were not included in trials. Clinical expertise is essential in determining how to manage these patients in practice.

<u>Reimbursement Considerations for Medicare (CMS) (Primarily DD-CKD Patients)</u>

The selection of treatments for patients at dialysis centers is already heavily constrained and driven by financial considerations. If roxadustat is approved by the FDA, CMS should seek to reimburse for its use in a way that creates more choice for patients and clinicians.

If roxadustat is covered outside of the ESRD bundle, CMS should consider carving out the treatment of anemia from the ESRD bundle so that selection of treatment can be on a competitive basis related to effectiveness and cost.

If roxadustat is covered inside the ESRD bundle, CMS should select reimbursement with a TDAPA (Transitional Drug Add-on Payment Adjustment) only under a new structure of linking the

additional reimbursement amount to demonstrated value, which would provide incentives for the manufacturer to generate better evidence of effectiveness. Reimbursement within the existing ESRD bundle base rate presents lower risk of creating perverse incentives that would overpay for treatment while limiting patient choice.

If roxadustat is to be covered within the ESRD bundle, CMS has two options to consider for reimbursement. One is to pay a TDAPA equal to its ASP. The second option is to include roxadustat within the ESRD bundle with no change to the base rate.

- ***Reimbursement with TDAPA***:
    - If CMS takes this approach, it may reward "innovation" in an existing functional category but roxadustat does not have evidence of superior performance to existing ESA options and, therefore, its claim to a TDAPA seems limited. In addition, providing any additional payment on top of the existing bundle would provide a perverse incentive for dialysis centers to favor the use of roxadustat solely for financial reasons.

If CMS chooses reimbursement with TDAPA, it should not use ASP as the basis for the payment. Instead, it should consider a demonstration project in which TDAPA is based on the relative added value of the new treatment. In this case, that would mean a $0 additional payment until further evidence is generated to demonstrate an added clinical value for roxadustat over ESAs.

- ***Reimbursement without change to the ESRD base rate:***
    - This option allows for greater competitive market forces to favor the more effective and/or lower cost agent. In addition, concern about lack of market opportunity for roxadustat is mitigated by its likely greater use in the private market for DI-CKD patients.
    - If evidence confirms that roxadustat is better than ESA, the bundle should be adjusted to accommodate a higher price based on incremental value to ESA. TDAPA should be reserved to treatments that demonstrate improvement over the existing treatments in the bundle.

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Supplemental Materials

A. Background: Supplemental Information

A1. Definitions

Anemia is defined as "a condition in which the number of red blood cells or their oxygen-carrying capacity is insufficient to meet physiological needs."[73] In anemia, insufficient numbers of circulating red blood cells or inadequate quantities of iron or functional Hb are available to transport and release oxygen to tissues. The World Health Organization (WHO) and the 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines define anemia as a Hb level of <12 g/dL in females and <13 g/dL in adult males. However, this definition does not provide goals of treatment for different patients' groups.[27,28]

CKD is a condition characterized by a gradual loss of kidney function over time. The definition and classification of CKD guidelines were established and endorsed by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) and the international KDIGO guideline group.[6,74-76] CKD is defined by the presence of kidney damage or decreased kidney function for three or more months.[77] Decreased kidney function refers to a decreased in GFR, which is usually estimated (eGFR) using serum creatinine and one of several available equations.[33,34,78] Patients who are diagnosed with CKD can be categorized into different stages according to the cause, their GFR (six G-stages; G-I: ≥90 ml/min per 1.73 m^2, G-II: 60-89, G-IIIa: 45-59, G-IIIb: 30-44, G-IV: 15-29, G-V: <15 ml/min per 1.73 m^2), and the amount of albumin or protein in the urine (three A-stages; A-1: <30, A-2: 30-299, and A-3: ≤300 mg/g). Additionally, patients with CKD can advance from being DI-CKD to renal failure (also known as ESKD), which is defined as severely reduced kidney function or treatment with dialysis (DD-CKD) or transplantation. Risk factors for CKD include genetic or sociodemographic predisposition, or the presence of diseases that can initiate and propagate kidney disease.

A2. Potential Cost-Saving Measures

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see https://icer.org/our-approach/methods-process/value-assessment-framework/). These services are ones that would not be directly affected by roxadustat (e.g., reduction in blood transfusion), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of CKD beyond the potential offsets that arise from a new intervention. During stakeholder engagement and public comment periods, ICER encouraged all stakeholders to suggest services (including treatments and mechanisms of care) currently used for patients with CKD that could be reduced, eliminated, or made more efficient. No suggestions were received.

B. Patient Perspectives: Supplemental Information

B1. Methods

ICER engaged with patients with CKD (DI-CKD, DD-CKD, and post-transplant), caregivers, representatives from professional and advocacy organizations, and clinical experts to understand the specific challenges associated with ongoing management of anemia in CKD from the patient perspective. ICER engaged with these groups using different platforms including webinars, one-on-one meetings, group meetings, and written communication.

C. Clinical Guidelines

Multiple organizations have issued guidelines about management of anemia in CKD. However, most of these guidelines are out of date and do not include roxadustat or any other HIF-PH inhibitors as potential treatment options.

Kidney Disease: Improving Global Outcomes

In 2012, KDIGO issued an anemia guideline, providing recommendations on treatment including the use of iron agents and ESAs.[79] Since then, KDIGO convened a Controversy Conference in December 2019 and had been planning a second one in 2020. These conferences aim to review the latest evidence and assess change implications for the 2012 KDIGO anemia guideline. Given that studies of the effects of HIF-PH inhibitors were still in progress, the first conference was focused on iron and target iron therapeutic agents. The second conference will be focused on ESAs and HIF-PH inhibitors; however, the conference has been postponed indefinitely due to the COVID-19 pandemic.

National Institute for Health and Care Excellence (NICE)

In 2015, NICE published their guidelines about anemia management in CKD, which did not include guidance about HIF-PH inhibitors.[80] Since then, NICE has conducted an update of the evidence in 2017 and concluded that there was no new evidence to issue recommendations about HIF-PH inhibitors as larger trials were underway. NICE was planning a scoping workshop in preparation for conducting an appraisal about roxadustat in March 2020, which was cancelled due to updates about the timing of the regulatory review.

D. Comparative Clinical Effectiveness: Supplemental Information

D1. Detailed Methods

Population, Intervention, Comparators, Outcomes, Timing, and Settings Framework (PICOTS)

Populations

The population of focus for this review is adults with anemia associated with CKD. We considered evidence across two relevant populations of patients:

1. Patients with DI-CKD
    - In population one, where data were available, we examined subgroups of patients defined by stages of CKD: G-stages III, IV, and V.
2. Patients with DD-CKD
    - In population two, we evaluated a subgroup of patients newly initiated on dialysis (incident DD-CKD).

We also considered other subgroups of interest defined according to iron status, inflammation status and ESA-hyporesponsiveness, presence of cardiovascular disease, or cancer.

Interventions

The intervention of interest is roxadustat (AstraZeneca).

Comparators

We sought evidence to compare roxadustat to:

- Darbepoetin alfa (Aranesp®, Amgen)
- Epoetin alfa (Epogen®, Amgen; Procrit®, Janssen)
- Methoxy polyethylene glycol-epoetin beta (Mircera®, Roche)
- Usual care (estimated by placebo arms of clinical trials)

Outcomes

We looked for evidence on the following outcomes of interest:

- Patient-important outcomes
    - All-cause mortality

    - Cardiovascular mortality
    - Stroke
    - MI
    - Unstable angina
    - Heart failure
    - Hospitalization
    - Blood transfusion
    - Rescue therapy
    - ESKD/kidney failure
    - HRQoL
    - Improvement in symptoms or function (e.g., fatigue, dyspnea)
    - Adverse events, including:
        - Serious adverse events
        - Treatment-emergent adverse events (TEAEs)
        - Adverse events (AEs) leading to treatment discontinuation
- Other outcomes
    - Anemia (as assessed by Hb and/or hematocrit)
    - Measures of iron storage and availability
    - Measures of inflammation
    - Lipid levels
    - CKD progression (as assessed by eGFR)

Timing

Evidence on intervention effectiveness and evidence on harms was derived from studies of any duration.

Settings

All relevant settings were considered, with a focus on outpatient settings in the US.

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on roxadustat for anemia in CKD followed established best research methods.[81,82] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[83] The PRISMA guidelines include a checklist of 27 items described further in Table D1.

Table D1. PRISMA 2009 Checklist

Checklist Items		
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured Summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and Registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility Criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information Sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study Selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data Collection Process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data Items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Risk of Bias in Individual Studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.
Summary Measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of Results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.
Risk of Bias Across Studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional Analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
RESULTS		
Study Selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study Characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of Bias Within Studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).

Checklist Items		
Results of Individual Studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of Results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of Bias Across Studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional Analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
DISCUSSION		
Summary of Evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

We searched MEDLINE and EMBASE for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms.

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see https://icer.org/policy-on-inclusion-of-grey-literature-in-evidence-reviews/).

Table D2. Search Strategy of MEDLINE via Ovid* for Roxadustat

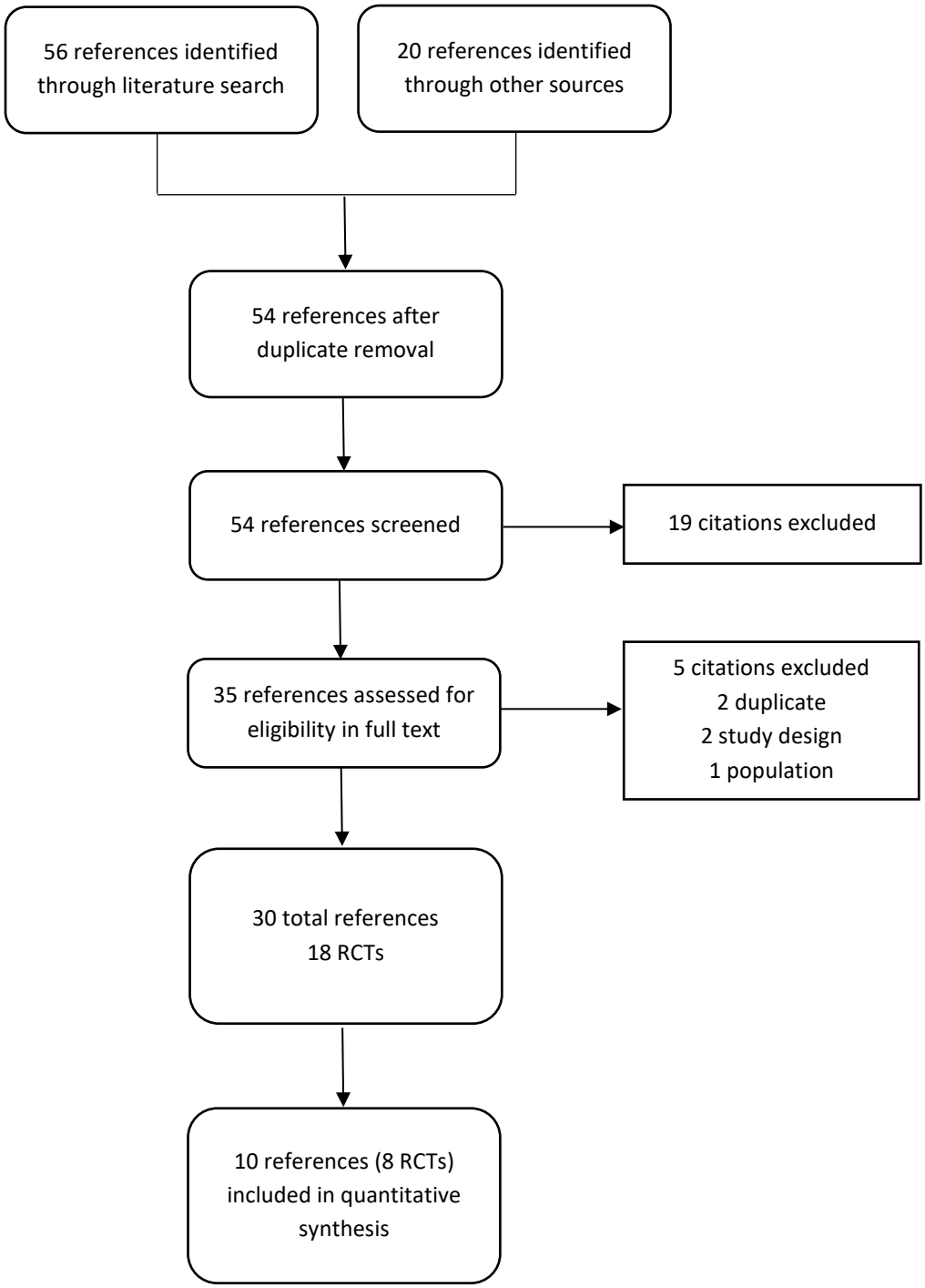
1	exp Anemia/ OR exp Anemia, Hypochromic/ OR exp Anemia, Refractory/
2	(an?emi* OR chronic anemia).ti,ab.
3	1 OR 2
4	exp Renal Insufficiency, Chronic/
5	(chronic kidney disease OR end*stage kidney disease OR end*stage kidney failure OR ESKD OR chronic renal disease OR end*stage renal dysfunction OR end*stage renal failure OR ESRD or stage 5 renal disease).ti,ab.
6	4 OR 5
7	3 AND 6
8	(roxadustat OR roxa OR FG-4592 OR FG4592 OR FG 4592 ASP-1517 OR ASP1517 OR ASP 1517 OR AZD-9941 OR AZD9941 OR AZD 9941 OR ai rui zhuo OR evrenzo).ti,ab.
9	7 AND 8
10	(addresses OR autobiography OR bibliography OR biography OR clinical trial, phase I OR comment OR congresses OR consensus development conference OR duplicate publication OR editorial OR guideline OR in vitro OR interview OR lecture OR legal cases OR legislation OR letter OR news OR newspaper article OR patient education handout OR periodical index OR personal narratives OR portraits OR practice guideline OR review OR video audio media).pt.
11	9 NOT 10
12	(exp animals/ OR exp animal/ OR exp nonhuman/ OR exp animal experiment/ OR animal model/ OR animal tissue/ OR non human/ OR (rat OR rats OR mice OR mouse OR swine OR porcine OR murine OR sheep OR lambs OR pigs OR piglets OR rabbit OR rabbits OR cat OR cats OR dog OR dogs OR cattle OR bovine OR monkey OR monkeys OR trout OR marmoset$1 OR basic research OR cell lines OR in vitro OR animal model OR canine).tw.) NOT (humans/ OR human/ OR human experiment/ OR (human* OR men OR women OR patients OR subjects).tw.)
13	11 NOT 12
14	limit 13 to english language
15	remove duplicates from 14

*Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to Present.

Table D3. Search Strategy of EMBASE for Roxadustat

#1	'anemia'/exp OR 'iron deficiency anemia'/exp OR 'refractory anemia'/exp OR 'refractory anemia with excess blasts'/exp
#2	'an?emi*':ti,ab OR 'chronic anemia':ti,ab
#3	#1 OR #2
#4	'chronic kidney failure'/exp OR 'end stage renal disease'/exp
#5	'chronic kidney disease':ti,ab OR 'end*stage kidney disease':ti,ab OR 'end*stage kidney failure':ti,ab OR 'ESKD':ti,ab OR 'chronic renal disease':ti,ab OR 'end*stage renal dysfunction':ti,ab OR 'end*stage renal failure':ti,ab OR 'ESRD':ti,ab OR 'stage 5 renal disease':ti,ab
#6	#4 OR #5
#7	#3 AND #6
#8	'roxadustat'/exp
#9	'roxadustat':ti,ab OR 'roxa':ti,ab OR 'fg-4592':ti,ab OR 'fg4592':ti,ab OR 'fg 4592':ti,ab OR 'asp-1517':ti,ab OR 'asp1517':ti,ab OR 'asp 1517':ti,ab OR 'azd-9941':ti,ab OR 'azd9941':ti,ab OR 'azd 9941':ti,ab OR 'ai rui rhuo':ti,ab OR 'evrenzo':ti,ab
#10	#8 OR #9
#11	#7 AND #10
#12	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp
#13	#11 NOT #12
#14	('case report'/de OR 'human tissue'/de OR 'nonhuman'/de OR 'practice guideline'/de OR 'questionnaire'/de OR 'chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
#15	#13 NOT #14
#16	#15 AND [english]/lim

Figure D1. PRISMA Flow Chart Showing Results of Literature Search for Roxadustat



Study Selection

We performed screening at both the abstract and full-text level. Two investigators independently screened all abstracts identified through electronic searches using DistillerSR (Evidence Partners, Ottawa, Canada) according to the inclusion and exclusion criteria described earlier. We did not exclude any study at abstract-level screening due to insufficient information. We retrieved the citations that were accepted during abstract-level screening for full-text appraisal. Two investigators reviewed full papers and provided justification for the exclusion of each excluded study.

Data Extraction and Quality Assessment

Two reviewers extracted key information from the full set of accepted trials. We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of clinical trials, using the categories "good," "fair," or "poor."[84] Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

Good: *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is paid to confounders in analysis. In addition, intention-to-treat (ITT) analysis is used for RCTs.*

Fair: *Studies were graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. ITT analysis is done for RCTs.*

Poor: *Studies were graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, ITT analysis is lacking.*

Note that case series are not considered under this rating system—because of the lack of comparator, these are generally considered to be of poor quality.

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus.[85,86]

Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. Given the emerging nature of the evidence base for newer treatments, we performed an assessment of publication bias for roxadustat using the clinicaltrials.gov database of trials. We scanned the site to identify studies completed more than two years ago that would have met our inclusion criteria and for which no findings have been published.

Data Synthesis and Statistical Analyses

Data on relevant outcomes were summarized in Evidence Tables and synthesized quantitatively and qualitatively in the body of the review. We evaluated the feasibility of conducting a quantitative synthesis by exploring the differences in study populations, study design, analytic methods, and outcome assessment for each outcome of interest. Based on the data availability from at least two sufficiently similar RCTs, we conducted random effect pairwise meta-analyses on the following outcomes: MI, stroke, unstable angina, heart failure, all-cause mortality, Short Form (SF)-36 Health Survey, Hb, any TEAE, serious TEAE, and discontinuation due to AEs. Effect sizes for continuous outcomes (e.g., Hb) were expressed as mean difference (MD) and 95% confidence intervals (95% CIs). For binary outcomes (e.g., all-cause mortality), we calculated risk ratios (RRs) and 95% CIs. We assessed heterogeneity used the Cochran q test and the I^2 statistic. To explore heterogeneity across studies, we examined differences in the distribution of key characteristics across studies, such as enrolled patients and baseline Hb. Due to inconsistent or limited reporting of data, other outcomes are described narratively only.

D2. Supplemental Results

Assessment of Bias

As described above, we searched for studies completed more than two years ago that would have met our inclusion criteria, and for which no findings have been published. For this review, we did not find any evidence for publication bias for completed trials of roxadustat. However, we identified five Phase III RCTs (NCT02021318, NCT02052310, NCT02174731, NCT02278341, and NCT02780726) and one Phase II RCT (NCT01888445) with interim results that have not been published in a peer-reviewed journal. Further, at the time of this report, only three of the key trials of roxadustat has been published.[18-20] Only interim data for the remaining key trials are available, and these results have not been published in a peer-reviewed journal.

Study Selection

Our literature search identified 76 potentially relevant references (see Figure D1), of which 19 references relating to 18 RCTs (11 publications, three clinical trial reports, two conference presentations, one conference abstract, one investor presentation, and one pre-approval AMCP dossier) and 18 references relating to pooled analyses of key Phase III RCTs (one publication, six conferences presentations, five conference posters, five conference abstracts, and one pre-approval AMCP dossier) met our inclusion criteria. The reasons for study exclusion were duplication, study type (non-comparative trial), and study population outside of our scope. Of the 34 included references, 17 references represented 18 RCTs of roxadustat, and 17 references represented pooled analyses of the key Phase III RCTs. One reference, the pre-approval AMCP dossier, represented both individual RCTs and pooled analyses in both populations. Additionally, results for ALPS, OLYMPUS, PYRENEES, and ROCKIES were also obtained from the clinicaltrials.gov database. Key trial details, including patient characteristics and clinical benefits, are presented below.

DI-CKD

A total of 12 references relating to two RCTs comparing roxadustat to darbepoetin alfa[21,38] and eight RCTs comparing roxadustat to placebo[18-20,22,26,39-43] met our inclusion criteria.

DD-CKD

A total of seven references (four publications, two clinical trial reports, and one pre-approval ACMP dossier) relating to one key Phase III RCT,[22,25] two additional Phase III RCTs,[40,44] and three Phase II RCTs met our inclusion criteria.[42,45,46] A total of two references (one investor presentation and one pre-approval AMCP dossier) relating to two key Phase III RCTs comparing roxadustat to epoetin alfa in incident dialysis (ID) and stable DD-CKD patients met our inclusion criteria.[22,26] A total of two references (one conference presentation and one pre-approval AMCP dossier) relating to one key Phase III RCT comparing roxadustat to epoetin alfa met our inclusion criteria.[22,24]

Quality of Individual Studies

We used the USPSTF criteria to rate the quality of the included RCTs.[84] Of note, we did not rate DOLOMITES and the 1517-CL-0310 RCT in the DI-CKD population and HIMALAYAS, PYRENEES, ROCKIES, SIERRAS, and the 1517-CL-0304 RCT in the DD-CKD population as they were only available in grey literature with limited reporting of details prohibiting evaluation of studies' quality.

In the DI-CKD population, Shutov 2021, Coyne 2020, Fishbane 2021, Chen 2019, and Chen 2017 were rated "good," and Besarab 2015 and Akizawa 2019 were rated "poor" due to lack of ITT analysis (see Table D5). In the DD-CKD population, Chen 2019 was rated "fair" while Akizawa 2020,

Provenzano 2016, and Chen 2017 were rated “poor” due to a lack of ITT analysis (see Table D4 on the following page).

Table D4. Study Quality of Included Trials

Trial	Comp. Groups	Non-Differential Lost to Follow-Up	Patient/ Investigator Blinding (Double-Blind)	Clear Def. of Intervention	Clear Def. of Outcomes	Selective Outcome Reporting	Measurements Valid	ITT Analysis	Approach to Missing Data	USPSTF Rating
Shutov 2021	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Multiple imputation	Good
Coyne 2020	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Multiple imputation	Good
Fishbane 2021	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Multiple imputation	Good
Chen 2019	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Multiple Imputation	Good
Besarab 2015	Yes	Unclear	No	Yes	Yes	No	Yes	No	LOCF	Poor
Chen 2017	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Unclear	Good
Akizawa 2019	Yes	Unclear	Yes	Yes	Yes	No	Yes	No	Unclear	Poor
Chen 2019	Yes	Unclear	No	Yes	Yes	No	Yes	Yes	Markov Chain Monte Carlo	Fair
Akizawa 2020	Yes	Unclear	Yes	Yes	Yes	No	Yes	No	Unclear	Poor
Provenzano 2016	Yes	Yes	No	Yes	Yes	No	Yes	No	Unclear	Poor
Chen 2017	Yes	Unclear	No	Yes	Yes	No	Yes	ITT	LOCF	Poor

Comp.: comparable, Def: definition, ITT: intention-to-treat, LOCF: last observation carried forward, USPSTF: United States Preventive Services Task Force

Trials of Roxadustat

DI-CKD

Key Trials of Roxadustat in the DI-CKD Population

We identified four Phase III, multicenter RCTs of roxadustat in DI-CKD.[18-21] The trials are described in detail below (Table D5 provides an overview of each trial, and additional trial details can be found in Evidence Table 1). ALPS, ANDES, and OLYMPUS have been published, and data for these trials and DOLOMITES were obtained from a clinical trial report, conference presentation, investor presentation, a pre-approval AMCP dossier, and the clinicaltrials.gov database (ALPS and OLYMPUS only).

DOLOMITES

The DOLOMITES trial was a multicenter, Phase III, open-label RCT conducted primarily in Europe that compared the safety and efficacy of roxadustat and darbepoetin alfa in 616 adults with DI-CKD III, IV, and V.[21] DOLOMITES included patients with Hb ≤10.50 g/dL. Patients with known NYHA Class III or IV congestive heart failure, MI, acute coronary syndrome, stroke, seizure or a thrombotic/thromboembolic event within 12 weeks, and uncontrolled hypertension were excluded from the trial. Patients were randomized to a weight-based starting dose of roxadustat three times weekly (n=323) or darbepoetin alfa (n=293) and treated for 104 weeks before a four-week follow-up period. Doses were titrated to correct and maintain Hb within 10.00 to 12.00 g/dL. Rescue therapy (blood transfusion, IV iron supplementation, and ESA treatment) was permitted. The patients had a mean age of 66 years, 45% were male, 14% were white, and mean Hb was 9.55 g/dL. Additional baseline characteristics can be found in Evidence Table 2.

The primary endpoint was Hb response, defined as Hb ≥11.00 g/dL and a Hb increase from baseline of 1.00 g/dL in patients with baseline Hb >8.00 g/dL, or an increase of ≥2.00 g/dL in patients with baseline Hb ≤8.00 g/dL, during the first 24 weeks of treatment without rescue therapy. Secondary endpoints included IV iron supplementation, HRQoL, CFB in Hb, and low-density lipoprotein (LDL)-cholesterol.

ALPS, ANDES, and OLYMPUS

The ALPS, ANDES, and OLYMPUS trials were global, multicenter, Phase III, double-blind RCTs that compared the safety and efficacy of roxadustat and placebo in adults with DI-CKD III, IV, and V.[18-20,22,26] ALPS and ANDES had similar inclusion criteria: Hb ≤10 g/dL, ferritin ≥30 ng/mL, and transferrin saturation (TSAT) ≥5%. OLYMPUS included patients with Hb <10.00g/dL, ferritin ≥50 ng/mL, and TSAT ≥15%. Patients who received ESA treatment within 12 weeks were excluded from ALPS and ANDES, while patients who received ESA treatment within six weeks were excluded from OLYMPUS. Patients with known NYHA Class III or IV congestive heart failure, MI, acute coronary

syndrome, stroke, seizure or a thrombotic/thromboembolic event with 12 weeks, and uncontrolled hypertension were excluded from the trials. Patients in ALPS and ANDES were randomized to a weight-based starting dose of roxadustat three times weekly (ALPS: n=394 and ANDES: n=616) or placebo (ALPS: 203 and ANDES: 306) and treated for 52 to 104 weeks in ALPS or up to four and a half years in ANDES (see Evidence Table 2). In OLYMPUS, patients were randomized to a starting dose of roxadustat 70 mg three times weekly (n=1,393) or placebo (n=1,388) and treated for up to four years. In all trials, the follow-up periods were four weeks, and doses were titrated to correct and maintain Hb within 10.00 to 12.00 g/dL. Rescue therapy was permitted. Baseline characteristics were similar across the trials (see Table D5 and Evidence Table 2).

The trials' primary endpoint was mean CFB in Hb averaged over weeks 28 to 52. Secondary endpoints included rescue therapy, blood transfusion, IV iron supplementation, hepcidin, ferritin, TSAT, and LDL-cholesterol.

Table D5. Key Trials of Roxadustat in DI-CKD

Trial (Number of Patients)	Treatment Arms	Key Baseline Characteristics
DOLOMITES (616)	Roxadustat TIW* Darbepoetin alfa	Mean age: 66 years Mean Hb: 9.55 g/dL Mean TSAT: NR Mean ferritin: NR Iron replete: 54% CRP >ULN: 37%
ALPS (594)	Roxadustat 70 or 100 mg TIW† Placebo	Mean age: 61 years Mean Hb: 9.09 g/dL Hepcidin: 39.51 ng/mL Mean TSAT: 25.55% Mean ferritin: 253.26 ng/mL Iron replete: 53% CRP >ULN: 35%
ANDES (922)	Roxadustat 70 or 100 mg TIW† Placebo	Mean age: 65 years Mean Hb: 9.10 g/dL Mean TSAT: 26.00% Mean ferritin: 307.64 ng/mL Iron replete: 60% CRP >ULN: 26%
OLYMPUS (2781)	Roxadustat 70 mg TIW Placebo	Mean age: 62 years Mean Hb: 9.10 g/dL Mean TSAT: NR Mean ferritin: NR Iron replete: 58% CRP >ULN: 16%

CRP: C-reactive protein, g/dL: grams per deciliter, Hb: hemoglobin, mg: milligram, NR: not reported, TIW: three times weekly, TSAT: transferrin saturation, ULN: upper limit of normal

*Weight-based starting dose not reported.

†Weight-based starting dose

Other Trials of Roxadustat in the DI-CKD Population

Phase III RCTs

The 1517-CL-0310 trial was a 52-week, multicenter, Phase III, open-label RCT that compared the efficacy and safety of roxadustat to darbepoetin alfa (comparative group) in 262 Japanese adults with DI-CKD III, IV, and V.[38] Patients who had received treatment with darbepoetin alfa or recombinant human erythropoietin were randomized to receive roxadustat for 52 weeks or darbepoetin alfa for 24 weeks. Additionally, patients who had received treatment with epoetin beta pegol were allocated to receive roxadustat (referential group) for 24 weeks. The trial included patients with Hb ≥10.0 g/dL and ≤12.0 g/dL and either TSAT ≥20% or ferritin ≥100 ng/mL who had been receiving ESA treatment by subcutaneous injection. Patients with NYHA Class III or IV congestive heart failure, history of hospitalization for treatment of stroke, MI, or pulmonary embolism within 12 weeks, or uncontrolled hypertension were excluded from the trial. At the time of this report, information regarding dosing and rescue therapy was not reported. The primary endpoint of the trial was mean CFB in Hb averaged over weeks 18 to 24. Secondary endpoints included the number of patients who achieved target Hb level and HRQoL. Baseline characteristics are unavailable at the time of this report.

Chen 2019 was a 26-week, multicenter, Phase III, double-blind RCT that compared the efficacy and safety of roxadustat and placebo in 154 Chinese adults with DI-CKD III, IV, and V.[40] The trial included patients with Hb ≥7 to <10 g/dL. Patients with ESA treatment within five weeks, NYHA Class III or IV congestive heart failure, or MI, acute coronary syndrome, stroke, seizure, or a thromboembolic event within 52 weeks, or uncontrolled hypertension were excluded from the trial. However, patients could be rescreened once hypertension was controlled. The trial consisted of two parts; in part one, patients were randomized to a weight-based starting dose of roxadustat 70 or 100 mg three times weekly or placebo for eight weeks; in part two, all patients received roxadustat for 18 weeks. Doses were increased every four weeks to maintain Hb ≥10.00 to ≤12.00 g/dL. Rescue therapy was permitted. The primary endpoint of the trial was mean CFB in Hb averaged over weeks seven to nine. Secondary endpoints included hepcidin, ferritin, TSAT, and LDL-cholesterol. The patients had a mean age of 54 years, 37% were male, and mean Hb was 8.90 g/dL. Additional baseline characteristics can be found in Evidence Table 3.

Phase II RCTs

Besarab 2015 was a four-week, Phase IIa, single-blind (patients), randomized, dose-ranging trial with a follow-period of up to 12 weeks that compared the efficacy and safety of roxadustat and placebo in 116 American adults with DI-CKD III and IV.[41] The trial included patients with Hb ≤11.0 g/dL. Patients with ESA treatment within 60 days, NYHA Class III or IV congestive heart failure, MI, or acute coronary syndrome within three months, thrombolytic events within four weeks, and uncontrolled hypertension were excluded from the trial. The trial consisted of a four-week

treatment period (day one to day 29 in patients treated with roxadustat two times weekly and day one to day 26 in patients treated with roxadustat three times weekly) and up to a 12-week follow-up period. Patients were sequentially enrolled to one of four roxadustat dose cohorts with administration two or three times weekly or placebo. Additional information on the roxadustat cohorts can be found in Evidence Table 1. A 50% dose reduction occurred when Hb increased ≥2.00 g/dL within any two-week period, while dosing was discontinued when the change in Hb was ≥3.00 g/dL at any assessment during the treatment period. Rescue therapy was prohibited during the treatment period and for the first four weeks of follow-up. However, it was permitted during the remainder of the follow-up period. Endpoints evaluated included Hb, hepcidin, and TSAT. The patients had a mean age of 66 years, 42% were male, and mean Hb was 10.30 g/dL. Additional baseline characteristics can be found in Evidence Table 4.

Chen 2017 was an eight-week, Phase II, parallel-arm, double-blind, dose-ranging RCT that compared the efficacy and safety of roxadustat and placebo in 91 Chinese adults with DI-CKD III, IV, and V.[42] The trial included patients with Hb <10.00 g/dL. Patients with ESA treatment within 12 weeks, NYHA Class III or IV congestive heart failure, or a thromboembolic event within 12 weeks were excluded from the trial. Patients were randomized to roxadustat or placebo three times weekly and then sequentially into roxadustat low dose (1.1 to 1.75 mg/kg) or high doses (1.50 to 2.3 mg/kg) using weight-based dosing. A dose-escalation could occur at week five, while dose reductions for excessive erythropoiesis could occur at any time. Rescue therapy with IV iron supplementation or ESA treatment was permitted if Hb <8.0 g/dL, and the investigator felt it was in the patient's medical interest. The primary endpoint was maximum CFB in Hb at any time from baseline to week eight. Secondary endpoints included hepcidin, transferrin, and TSAT. The patients had a mean age of 50 years, 59% were male, and mean Hb was 8.80 g/dL. Additional baseline characteristics can be found in Evidence Table 4.

Akizawa 2019 was a 24-week, multicenter, Phase II, parallel-arm, double-blind RCT that compared the efficacy and safety of roxadustat and placebo in 107 Japanese adults with CKD not on dialysis for three months since trial completion.[43] The trial included patients with Hb <10.00g g/dL and ferritin ≥30 ng/mL and TSAT ≥5%. Patients with ESA treatment within six weeks, NYHA Class III or IV congestive heart failure, history of hospitalization for stroke, MI, or lung infarction within 24 weeks, or uncontrolled hypertension were excluded from the trial. Patients were randomized to three active treatment arms of either roxadustat 50, 70, or 100 mg three times weekly or placebo for six weeks (fixed-dose period), followed by dose adjustments to maintain Hb 10.00 to 12.00 g/dL for 18 weeks (titration period). Patients meeting pre-defined criteria were re-randomized to three times weekly or one-time, weekly dosing. IV iron supplementation was permitted if serum ferritin was <30 ng/mL and TSAT was <5%. The primary endpoint was the mean rate of rise in Hb up to week six. Secondary endpoints included hepcidin, transferrin, and TSAT. The patients had a mean age of 64 years, 83% were male, and mean Hb was 9.38 g/dL. Additional baseline characteristics can be found in Evidence Table 4.

DD-CKD

Key Trials of Roxadustat in the DD-CKD Population

HIMALAYAS, PYRENEES, ROCKIES, and SIERRAS

We identified four Phase III, multicenter RCTs of roxadustat in DD-CKD.[22,24-26] The trials are described in detail below (Table D7 provides an overview of each trial, and additional trial details can be found in Evidence Table 17). All RCTs are currently unpublished, and data for these studies was obtained from a clinical trial report, conference presentation, investor presentation, a pre-approval AMCP dossier, and the clinicaltrials.gov database (PYRENEES and ROCKIES only).

The HIMALAYAS, ROCKIES, and SIERRAS trials were multicenter, Phase III, open-label RCTs that compared the efficacy and safety of roxadustat to epoetin alfa in adults with incident DD-CKD (HIMALAYAS) or incident and stable DD-CKD (ROCKIES and SIERRAS).[22,24,26] The key RCTs defined incident and stable DD-CKD as receiving dialysis for two weeks to ≤4 months and >4 months, respectively, prior to randomization. While HIMALAYAS and ROCKIES were global trials, SIERRAS was conducted in the US and Latin America. The PYRENEES trial was a multicenter, Phase III, open-label RCT conducted in Europe that compared the safety and efficacy of roxadustat to darbepoetin alfa and epoetin alfa, where most results for the comparators were presented in a pooled ESA treatment arm.[22,25]

HIMALAYAS included patients receiving hemodialysis (HD) or peritoneal dialysis (PD) ≥2 weeks to ≤4 months, Hb ≤10.00 g/dL, and ferritin ≥100 ng/mL and TSAT ≥20%. PYRENEES included patients receiving hemodiafiltration, HD, or PD for ≥4 months, Hb 9.50 to 12.00 g/dL, and receiving ESA treatment ≥8 weeks. ROCKIES included patients receiving HD or PD ≥2 weeks, Hb <12.00 g/dL (if receiving ESA treatment), and Hb <10.00 g/dL (if not receiving ESA treatment), ferritin ≥100 ng/mL, and TSAT ≥20%. SIERRAS included patients receiving HD or PD. Further, stable DD-CKD patients were eligible if their Hb was ≥9.00 to ≤12.00 g/dL, and they had been receiving ESA treatment ≥8 weeks, while incident DD-CKD patients were eligible if their Hb was ≥8.5 to ≤12.0 g/dL and they had been receiving ESA treatment ≥4 weeks. Additional eligibility criteria for SIERRAS included ferritin ≥100 ng/mL and TSAT ≥20%. Patients receiving ESA treatment ≤3 weeks in the previous three months, congestive heart failure, MI, stroke, or blood clots within a major vessel, or uncontrolled hypertension were excluded from HIMALAYAS. PYRENEES, ROCKIES, and SIERRAS excluded patients with known NYHA Class III or IV congestive heart failure, MI, acute coronary syndrome, stroke, seizure, or a thrombotic/thromboembolic event with 12 weeks. Patients were randomized to a weight-based starting dose of roxadustat or epoetin alfa or ESA (PYRENEES only) and treated for up to four years (Evidence Table 17). Doses were titrated to maintain Hb, and rescue therapy (blood transfusion and ESA treatment) was permitted. IV iron supplementation was administered per usual care with ESAs and was limited to rescue therapy with roxadustat. Key baseline characteristics are shown in Table D6. Mean Hb at baseline was highest in PYRENEES, followed by

SIERRAS, ROCKIES, HIMALAYAS (see Table D6). Additionally, 100% of patients in HIMALAYAS had incident DD-CKD, while in ROCKIES, 20% of patients had incident DD-CKD and in SIERRAS, 10% of patients had incident DD-CKD (see Table D6).

The primary endpoint of all the trials was mean CFB in Hb averaged over weeks 28 to 52. Secondary endpoints included rescue therapy, blood transfusion, IV iron supplementation, hepcidin, ferritin, and LDL-cholesterol.

Table D6. Key Trials of Roxadustat in DD-CKD

Trial (Number of Patients)	Population	Treatment Arms	Key Baseline Characteristics*
HIMALAYAS (1043)	Incident DD-CKD	Roxadustat 70 or 100 mg TIW† Epoetin alfa	Mean age: 54 years Incident DD-CKD: 100% Mean Hb: 8.45 g/dL Mean TSAT: 27.29% Ferritin: 430.00 ng/mL CRP >ULN: 52%
PYRENEES (836)	Stable DD-CKD	Roxadustat 70 or 100 mg TIW‡ ESAs	Mean age: 61 years Incident DD-CKD: 0% Mean Hb: 10.77 g/dL Mean TSAT: NR Mean ferritin: NR CRP >ULN: NR
ROCKIES (2133)	Incident and stable DD-CKD	Roxadustat 70, 100, 150, or 200 mg TIW‡ Epoetin alfa	Mean Age: 54 years Incident DD-CKD: 20% Mean Hb: 9.10 g/dL Mean TSAT: NR Mean ferritin: NR CRP >ULN: NR
SIERRAS (741)	Incident and stable DD-CKD	Roxadustat 70, 100, 150, or 200 mg TIW‡ Epoetin alfa	Mean age: NR Incident DD-CKD: 10% Mean Hb: 10.25 g/dL Mean TSAT: NR Mean ferritin: NR CRP >ULN: 49%

CKD: chronic kidney disease, CRP: C-reactive protein, DD: dialysis-dependent, ESA: erythropoiesis-stimulating agents, g/dL: grams per deciliter, Hb: hemoglobin, mg: milligram, NR: not reported, TIW: three times weekly, TSAT: transferrin saturation, ULN: upper limit of normal

*No key trials reported baseline hepcidin or CRP levels or iron-repletion status.

†Weight-based starting dose.

‡Starting dose varied based on weight and prior ESA use.

Other Trials of Roxadustat in the DD-CKD Population

Phase III RCTs

Chen 2019 was a 26-week, multicenter, Phase III, open-label RCT that compared roxadustat to epoetin alfa in 305 Chinese adults with stable DD-CKD.[40] The trial included patients with Hb 9.00 to

12.00 g/dL receiving HD or PD ≥16 weeks and stable doses of epoetin alfa ≥6 weeks. Patients with NYHA Class III or IV congestive heart failure, or MI, acute coronary syndrome, stroke, seizure, or thromboembolic event within 52 weeks were excluded from the trial. Patients were randomized to either a weight-based starting dose of roxadustat (100 or 120 mg three times weekly) (n=204) or epoetin alfa (n=101) for 26 weeks. Doses were adjusted to maintain Hb 10.00 to 12.00 g/dL. Rescue therapy was permitted in patients with Hb <8.00 g/dL or in patients with Hb <9.00 g/dL who had a confirmed decrease from baseline of >1.00 g/dL. The patients had a mean age of 54 years, 59% were male, and mean Hb was 8.45 g/dL. Additional baseline characteristics can be found in Evidence Table 19. The primary endpoint of the trial was mean CFB in Hb averaged over weeks 23 to 27. Secondary endpoints included hepcidin, transferrin, and TSAT.

Akizawa 2020 was a 24-week, multicenter, Phase III, double-blind, double-dummy, parallel-arm RCT that compared roxadustat to darbepoetin alfa in 303 adults with stable DD-CKD.[44] The trial included patients with Hb ≥10.00 to ≤12.0 g/dL receiving HD >12 weeks and recombinant human erythropoietin or darbepoetin alfa >8 weeks with either ferritin ≥100 ng/mL or TSAT ≥20%. Patients with NYHA Class III or IV congestive heart failure, history of hospitalization for treatment of stroke, MI, or pulmonary embolism within 12 weeks were excluded from the trial. Patients were randomized to either roxadustat three times weekly (n=151) or darbepoetin alfa one time weekly (n=152) based on the average pre-randomization weekly dose of recombinant human erythropoietin or darbepoetin alfa for up to 24 weeks. While there was no formal washout period, the treatment period began on the day of dialysis after the longest dialysis interval in the week when ESA had been administered (i.e., within one to two weeks). Doses were titrated to maintain Hb 10.00 to 12.00 g/dL. IV iron was permitted at the discretion of the investigator only to maintain ferritin ng/mL ≥100 and/or TSAT ≥20% when ferritin was <100 ng/ml or TSAT was <20%. The patients had a mean age of 65 years, 69% were male, and mean Hb was 11.02 g/dL. Additional baseline characteristics can be found in Evidence Table 19. The primary endpoint was mean CFB in Hb averaged over weeks 18 to 24. Secondary endpoints included hepcidin, transferrin, and TSAT.

Phase II RCTs

Provenzano 2016 was a six to 19 week, multicenter, Phase II, open-label, randomized, dose-ranging trial that compared roxadustat to epoetin alfa in 144 American adults with stable DD-CKD.[45] The trial included patients with Hb 9.00 to 13.50 g/dL receiving HD ≥4 months and epoetin alfa for four weeks. Patients who received any ESA other than epoetin alfa within 12 weeks, NYHA Class III or IV congestive heart failure, MI within three months, or a thromboembolic event within 12 weeks were excluded from the trial. The trial consisted of two parts: in part one, patients were randomized to four cohorts of roxadustat (n=41) 1.0, 1.5, 1.8, or 2.0 mg/kg three times weekly or epoetin alfa (n=13) for six weeks with an eight-week follow-up period. Results from part one were used to inform optimal starting doses of roxadustat in part two. In part two, patients were randomized to 6.5 cohorts of roxadustat with various starting doses (n=67) or continuation of epoetin alfa (n=23)

for 19 weeks with a four-week follow-up period. During the follow-up periods, patients randomized to roxadustat were switched back to epoetin alfa. Rescue therapy was permitted. The patients had a mean age of 58 years, 67% were male, 59% were white, and mean Hb was 11.40 g/dL. Additional baseline characteristics can be found in Evidence Table 20. The primary endpoint in part one was the proportion of patients whose Hb did not decrease ≥0.5 g/dL from baseline, while the primary endpoint in part two was the proportion of patients whose mean Hb was ≥11.0 g/dL over the last four weeks of treatment. Secondary endpoints included hepcidin and TSAT.

Chen 2017 was a seven-week, multicenter, Phase II, parallel-arm, open-label, randomized, dose-ranging trial that compared roxadustat to epoetin alfa in 87 Chinese adults with stable DD-CKD.[42] Patients were stratified by baseline epoetin alfa dose and randomized to roxadustat three times weekly or epoetin alfa (n=22). Patients randomized to roxadustat were sequentially enrolled to low (1.10 to 1.80 mg/kg; n=22), medium (1.50 to 2.30 mg/kg; n=21), or high (1.70 to 2.30 mg/kg; n=22) doses of roxadustat. Dose titration was permitted to maintain Hb, where doses could be increased at week five, and dose decreases were permitted at any time during the dosing period for protocol-defined excessive erythropoiesis. Rescue therapy was permitted if Hb was <8.00 g/dL or <9.00 g/dL with a ≥1.50 g/dL decrease from baseline. The patients had a mean age of 51 years, 60% were male, and mean Hb was 10.70 g/dL. Additional baseline characteristics can be found in Evidence Table 20. The primary endpoint was the percentage of subjects with successful dose conversion, defined as a Hb level maintained at <0.5g/dL below mean baseline value during the last two weeks of the six-week dosing period in the efficacy evaluable population. Secondary endpoints included hepcidin, transferrin, and TSAT.

The 1517-CL-0304 trial was a multicenter, Phase II, parallel-arm, double-blind (arms one to three), open-label (arm four) RCT that compared roxadustat to darbepoetin alfa in 130 Japanese adults with stable DD-CKD.[46] The trial consisted of three parts: part one was a fixed-dose period from the start of treatment to week six; part two was a titration period from week six to week 24, and part three was a four-week follow-up period. Patients were randomized to one of four arms: roxadustat 50 mg three times weekly (n=33), roxadustat 70 mg three times weekly (n=32), roxadustat 100 mg three times weekly (n=33), or darbepoetin alfa (n=32). Though IV iron supplementation was reported, additional information regarding the administration of rescue therapy is unavailable at the time of this report. The patients had a mean age of 62 years, 73% were male, and mean Hb was 8.83 g/dL. Additional baseline characteristics can be found in Evidence Table 20. The primary endpoint was CFB in the rate of rise in Hb to the final assessment of the fixed-dose period. Secondary endpoints included Hb.

Clinical Benefits of Roxadustat

The clinical benefits and harms of roxadustat are first detailed in the DI-CKD population, followed by the DD-CKD population.

DI-CKD

Cardiovascular Safety

As described above, the key RCTs were designed with Hb as the primary endpoint; thus, the number of cardiovascular events was low (see Evidence Table 11).

DOLOMITES RCT (roxadustat vs. darbepoetin alfa): At the time of this report, only DOLOMITES reported adjudicated cardiovascular events (see Table D7).[21] Due to the small sample size, the results were a non-confirmatory analysis. There were no significant differences in the risk of major adverse cardiovascular events (MACE: all-cause mortality, MI, or stroke), MACE+ (MACE, unstable angina requiring hospitalization, or congestive heart failure requiring hospitalization), or all-cause mortality with roxadustat compared to darbepoetin alfa during the safety emergent period (see Table D7). Additionally, there were no significant differences in the risk of first MI, stroke, unstable angina requiring hospitalization, or congestive heart failure requiring hospitalization (see Table D7).

Table D7. Adjudicated Cardiovascular Events in DOLOMITES

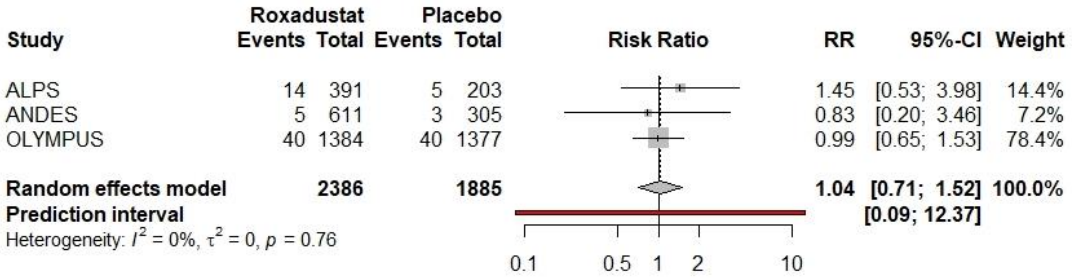
Outcomes	Arms		Between Group Differences
	Roxadustat (N=323)	Darbepoetin Alfa (N=293)	HR (95% CI)
MACE, n (%)	38 (11.8)	41 (14.0)	0.81 (0.52, 1.25)
MACE+, n (%)	54 (16.7)	53 (18.1)	0.90 (0.61, 1.32)
All-Cause Mortality, n (%)	29 (9.0)	31 (10.6)	0.83 (0.50, 1.38)
MI, n (%)	11 (3.4)	10 (3.4)	0.96 (0.41, 2.27)
Stroke, n (%)	4 (1.2)	7 (2.4)	0.48 (0.14, 1.67)
Unstable Angina Requiring Hospitalization, n (%)	0 (0.0)	1 (0.3)	--
Congestive Heart Failure Requiring Hospitalization	25 (7.7)	21 (7.2)	1.08 (0.60, 1.95)

95% CI: 95% confidence interval, HR: hazard ratio, MI: myocardial infarction, N: total number, MACE: major adverse cardiovascular event (all-cause mortality, MI, or stroke), MACE+: MACE, unstable angina requiring hospitalization, or congestive heart failure requiring hospitalization

ALPS, ANDES, and OLYMPUS RCTs (roxadustat vs. placebo): While adjudicated cardiovascular events were not reported for these RCTs, the incidence of several cardiovascular safety events was reported. We performed a meta-analysis of MI reported for ALPS, ANDES, and OLYMPUS.[18,19,23] As

seen in Figure D2, the meta-analysis results suggest that the risk of MI is not significantly different with roxadustat compared to placebo (RR: 1.04; 95% CI: 0.71 to 1.52; I^2=0%).

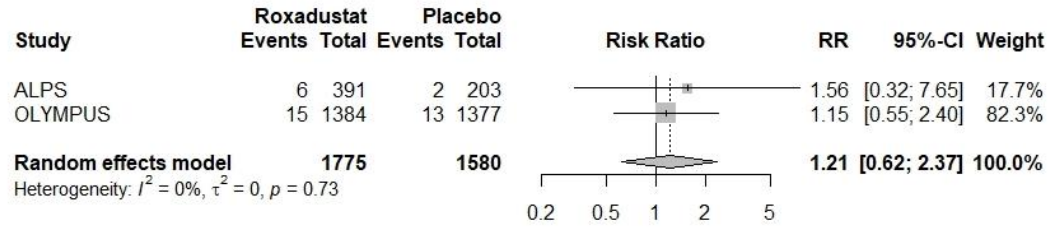
Figure D2. Meta-Analysis of MI in ALPS, ANDES, and OLYMPUS



95% CI: 95% confidence interval, I^2: I-squared, RR: risk ratio, τ^2: between-study-variance estimator

We also performed a meta-analysis of stroke reported for ALPS and OLYMPUS.[23,49] As seen in Figure D3, the meta-analysis results suggest that the risk of stroke is not significantly different with roxadustat compared to placebo (RR: 1.21; 95% CI: 0.62 to 2.37; I^2=0%).

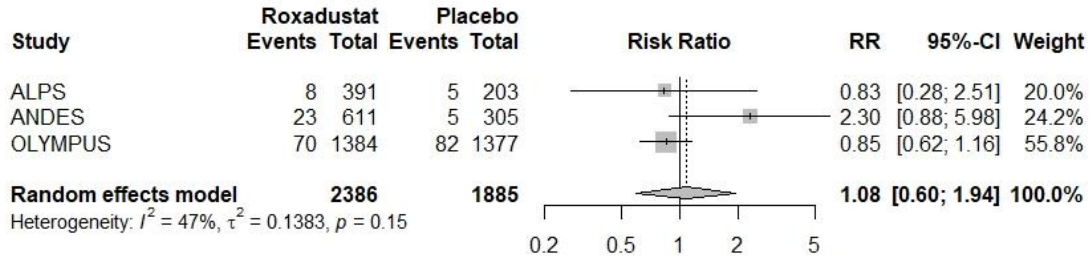
Figure D3. Meta-Analysis of Stroke in ALPS and OLYMPUS



95% CI: 95% confidence interval, I^2: I-squared, RR: risk ratio, τ^2: between-study-variance estimator

We performed a meta-analysis of heart failure reported for ALPS, ANDES, and OLYMPUS.[18,19,23] As seen in Figure D4, the meta-analysis results suggest that the risk of heart failure is not significantly different with roxadustat compared to placebo (RR: 1.08; 95% CI: 0.60 to 1.94; I^2=47%).

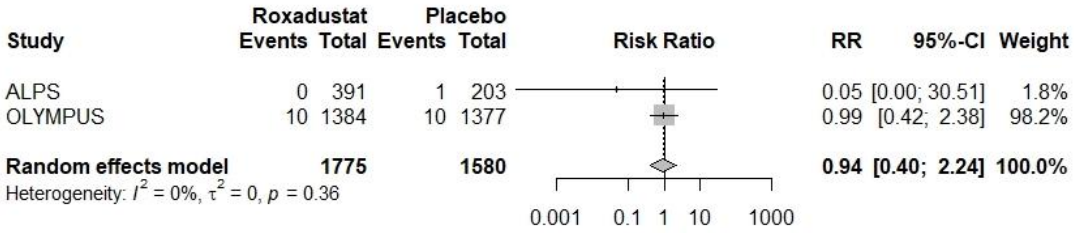
Figure D4. Meta-Analysis of Heart Failure in ALPS, ANDES, and OLYMPUS



95% CI: 95% confidence interval, I^2: I-squared, RR: risk ratio, τ^2: between-study-variance estimator

Finally, we performed a meta-analysis of unstable angina reported for ALPS and OLYMPUS.[19,23] As seen in Figure D5, the meta-analysis results suggest that the risk of unstable angina is not significantly different with roxadustat compared to placebo (RR: 0.94; 95% CI: 0.40 to 2.24; I^2=0%).

Figure D5. Meta-Analysis of Unstable Angina in ALPS and OLYMPUS

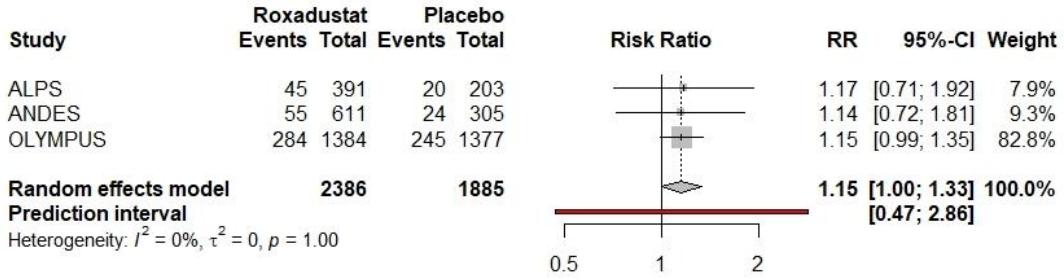


95% CI: 95% confidence interval, I^2: I-squared, RR: risk ratio, τ^2: between-study-variance estimator

Further, a pooled analysis of the ITT populations of ALPS, ANDES, and OLYMPUS reported that roxadustat was not significantly different from placebo in the risk of MACE (hazard ratio [HR]: 1.08; 95% CI: 0.94 to 1.24), MACE+ (HR: 1.04; 95% CI: 0.91 to 1.18), or all-cause mortality (HR: 1.06; 95% CI: 0.91 to 1.23) during the study period.[17] Moreover, there was no significant difference in the risk of hospitalization for congestive heart failure (HR: 0.89; 95% CI: 0.72 to 1.12).[68]

However, the HR for all-cause mortality reported above was based on all deaths during the study period, including deaths in patients no longer on therapy. At the time of this report, the data used to pool the HR for this outcome are unavailable. Thus, we also performed a meta-analysis of available data for all-cause mortality.[19,20,22,23] As seen in Figure D6, the meta-analysis found an increased risk of all-cause mortality with roxadustat of borderline statistical significance (risk ratio [RR]: 1.15; 95% CI: 1.00 to 1.33; I^2=0%). While all-cause mortality reported for ALPS appears to have been up to 28 days after the last dose of study drug (available sources currently disagree slightly on these numbers), all-cause mortality reported for OLYMPUS was up to and including the end of study visit or date of last contact or withdrawal of consent. The timepoint in which all-cause mortality was reported for ANDES is unclear at the time of this report. The reported HR for mortality up to 28 days after the last dose of study drug was 0.96; 95% CI: 0.53 to 1.74,[20] which is substantially lower than the RR of 1.17; this suggests that the RR calculations may be overestimating risk that takes into account time of exposure to therapy and time to events.

Figure D6. Meta-Analysis of All-Cause Mortality for ALPS*, ANDES, and OLYMPUS



95% CI: 95% confidence interval, I^2: I-squared, RR: risk ratio, τ^2: between-study-variance estimator
*We note disagreement among sources.

Other RCTs had shorter durations and were not powered to detect significant differences in cardiovascular events and reported low event rates (see Evidence Table 12 and Evidence Table 13).

HRQoL

The RCTs assessed HRQoL with the SF-36 Health Survey,[87] European Quality of Life Questionnaire-5 Dimensions-5 Levels (EQ-5D-5L) Visual Analogue Scale (VAS),[88] Functional Assessment of Cancer Therapy-Anemia (Fact-An),[89] and Patients' Global Impression of Change (PGIC).[90]

Higher scores on SF-36, EQ-5D-5L, and Fact-An indicate better quality of life. In the PGIC, patients rate their change as "very much improved," "much improved," "minimally improved," "no change," "minimally worse," "much worse," or "very much worse."

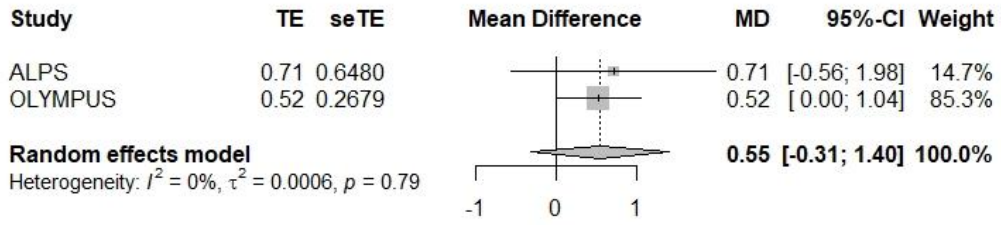
SF-36

DOLOMITES RCT (roxadustat vs. placebo): Patients receiving roxadustat had a significant decline in SF-36 Physical Functioning (PF) sub-score averaged over weeks 12 to 28 (least squares means [LSM] difference: -1.28; 95% CI: -2.42 to -0.15) compared with those on darbepoetin alfa.[21] However, this difference did not exceed the minimum clinically important difference (MCID) of 3 to 5 points.[47] There was no significant difference between roxadustat and darbepoetin alfa in mean CFB in SF-36 Vitality (VT) sub-score averaged over weeks 12 to 28 (LSM difference: -0.46; 95% CI: -1.66 to 0.74).[21]

ALPS, ANDES, and OLYMPUS RCTs (roxadustat vs. placebo): A pooled analysis of ANDES, ALPS, and OLYMPUS reported a significant increase in mean CFB in SF-36 PF sub-score at week 12 with roxadustat compared to placebo (LSM difference: 0.53; 95% CI: 0.05 to 1.01).[48] However, we performed a meta-analysis of this outcome averaged over weeks 12 to 28 for ALPS and OLYMPUS.[19,20,23] As seen in Figure D7, the meta-analysis results demonstrate no significant difference with roxadustat compared to placebo (MD: 0.55; 95% CI: -0.31 to 1.40; I^2=0%).

In ALPS, there was no significant difference in mean CFB in SF-36 Physical Component sub-score averaged over weeks 12 to 28 with roxadustat compared to placebo (LSM difference: 0.37; 95% CI: -0.65 to 1.40).[23]

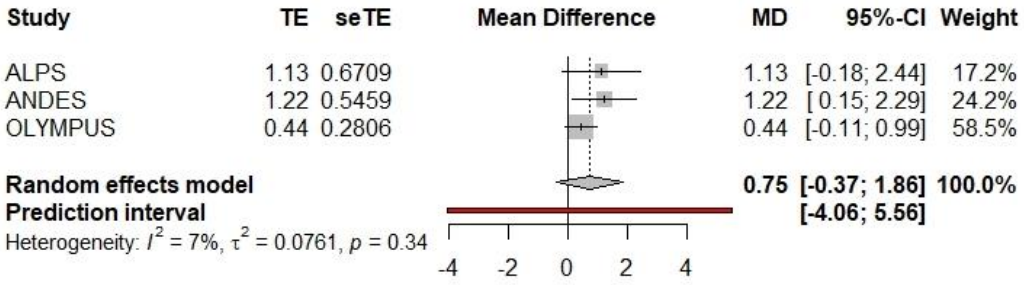
Figure D7. Meta-Analysis of SF-36 Health Survey PF for ALPS and OLYMPUS



95% CI: 95% confidence interval, I^2: I-squared, MD: mean difference, seTE: standard error, τ^2: between-study-variance estimator, TE: effect size

Further, the pooled analysis also reported a significant increase in mean CFB in SF-36 VT sub-score at 12 weeks with roxadustat compared to placebo (LSM difference: 0.96; 95% CI: 0.44 to 1.47).[48] However, we performed a meta-analysis of this outcome averaged over weeks 12 to 18 for ALPS ANDES, and OLYMPUS.[18-20] As seen in Figure D8, the meta-analysis results demonstrate no significant difference with roxadustat compared to placebo (MD: 0.75; 95% CI: -0.37 to 1.86; I^2=7%).

Figure D8. Meta-Analysis of SF-36 Health Survey VT for ALPS, ANDES, and OLYMPUS



95% CI: 95% confidence interval, I^2: I-squared, MD: mean difference, seTE: standard error, τ^2: between-study-variance estimator, TE: effect size

Further, a MCID of 3 to 5 points was not reached in SF-36 PF or VT sub-scores.[47] Because there were no significant differences in these endpoints averaged over weeks 12 to 28 in individual RCTs, it unclear if the differences reported for the pooled analysis would also lack statistical significance at later timepoints.

EQ-5D-5L VAS

In ALPS, mean CFB in the EQ-5D-5L VAS score averaged over weeks 12 to 28 was numerically greater with roxadustat compared to placebo (MD: 5.39 ± 17.28 vs. 0.99 ± 15.86); however,

statistical values were not reported.[23] In the pooled analysis, mean CFB in the EQ-5D-5L VAS score was significantly greater at week 12 with roxadustat compared to placebo (LSM difference: 1.68; 95% CI: 0.76 to 2.59).[48] While a MCID for EQ-5D-5L VAS score has not been established in patients with CKD, in stroke patients undergoing rehabilitation,[91] oncology patients,[92] and patients with chronic obstructive pulmonary disease (COPD),[93] a MCID ranged from 8 to 12 points.

FACT-An

In ALPS, mean CFB in Total FACT-An score averaged over weeks 12 to 28 was significantly greater with roxadustat compared to placebo (LSM difference: 1.70; 95% CI: 0.02 to 3.38).[23] In the pooled analysis, mean CFB in Total FACT-An score was significantly greater at week 12 with roxadustat compared to placebo (LSM difference: 1.81; 95% CI: 0.52 to 3.08).[48]

Further, in ALPS, there was no significant difference in mean CFB in FACT-An Anemia Subscale (AnS) sub-score averaged over weeks 12 to 28 with roxadustat compared to placebo (LSM difference: 2.09; 95% CI: -1.29 to 5.46).[23] In the pooled analysis, mean CFB in FACT-An AnS sub-score was significantly greater at week 12 with roxadustat compared to placebo (LSM difference: 1.70; 95% CI: 0.02 to 3.38).[48] Importantly, MCIDs of 6 points and 4 points for Total FACT-An and FACT-An AnS, respectively, were not reached.[94]

PGIC

In ALPS, the proportion of patients who rated their status as "very much improved" or "much improved" at week 28 was numerically greater with roxadustat compared to placebo (46.4% vs. 28.6%); however, statistical values were not reported.[23] In the pooled analysis, the proportion of patients who rated their status as "very much improved" or "much improved" was significantly greater at week 12 with roxadustat compared to placebo (odds ratio difference: 2.03; 95% CI: 1.74 to 2.36).[48]

Rescue Therapy

DOLOMITES RCT (roxadustat vs. darbepoetin alfa): Data regarding the composite rescue therapy endpoint and blood transfusion is unavailable at the time of completing this report. However, the risk of IV iron supplementation was significantly reduced with roxadustat compared to darbepoetin alfa in the first 36 weeks (HR: 0.45; 95%: CI: 0.26 to 0.78).[21]

ALPS, ANDES, and OLYMPUS RCTs (roxadustat vs. placebo): The risk of rescue therapy was significantly reduced with roxadustat compared to placebo in ALPS and ANDES in the first 52 weeks and in OLYMPUS on treatment plus 28 days (see Table D8). This was demonstrated in a pooled analysis of these RCTs at 52 weeks (HR: 0.19; 95% CI: 0.16 to 0.23).[17]

Similarly, the risk of blood transfusion was significantly reduced with roxadustat compared to placebo in ALPS and ANDES in the first 52 weeks and in OLYMPUS on treatment plus 28 days (see Table D8). This was also demonstrated in a pooled analysis of these RCTs at 52 weeks (HR: 0.26; 95% CI: 0.21 to 0.32).[17,22,95]

The risk of IV iron supplementation was significantly reduced with roxadustat compared to placebo in ALPS at 104 weeks (HR: 0.54; 95% CI: 0.29 to 0.99), ANDES at 52 weeks (HR: 0.39; 95% CI: 0.19 to 0.81), and in OLYMPUS on treatment plus 28 days (HR: 0.41; 95% CI: 0.29 to 0.56) compared to placebo.[18,19,23]

The risk of ESA treatment was significantly reduced with roxadustat compared to placebo in ALPS at 104 weeks (HR: 0.10; 95% CI: 0.06 to 0.17), ANDES at 52 weeks (HR: 0.08; 95% CI: 0.04 to 0.15) and in OLYMPUS on treatment plus 28 days (HR: 0.13; 95% CI: 0.10 to 0.18).[18,19,23]

Table D8. Rescue Therapy in DOLOMITES, ALPS, ANDES, and OLYMPUS

Trial	DOLOMITES		ALPS		ANDES		OLYMPUS	
	ROX (N=323)	DA (N=293)	ROX (N=323)	PBO (N=203)	ROX (N=616)	PBO (N=306)	ROX (N=1384)	PBO (N=1376)
Risk of Rescue Therapy,* HR (95% CI)	NR		0.24 (0.17, 0.33)*		0.19 (0.14, 0.28)*		0.26 (0.23, 0.31)#	
Risk of Blood Transfusion, HR (95% CI)	NR		0.34 (0.21, 0.55)*		0.26 (0.17, 0.41)*		0.37 (0.30, 0.44)#	
Risk of IV Iron Supplementation, HR (95% CI)	0.45 (0.26, 0.78)†		0.54 (0.29, 0.99)‡		0.39 (0.19, 0.81)*		0.41 (0.29, 0.56)#	
Risk of ESA Treatment, HR (95% CI)	NR		0.10 (0.06, 0.17)‡		0.08 (0.04, 0.15)*		0.13 (0.10, 0.18)#	

95% CI: 95% confidence interval, DA: darbepoetin alfa ESA: erythropoiesis-stimulating agent, IV: intravenous, HR: hazard ratio, N: total number, NR: not reported, PBO: placebo, ROX: roxadustat

*At 52 weeks.

†At 36 weeks.

‡At 104 weeks.

#On treatment plus 28 days.

In general, a reduction in the use of rescue therapy was observed with roxadustat compared to placebo in the other RCTs. In Chen 2019, there was a significant reduction in the use of rescue therapy with roxadustat compared to placebo (HR: 0.11; 95% CI: 0.02 to 0.51).[40] Chen 2017 reported a numerical reduction in the use of rescue therapy with roxadustat compared to placebo (pooled roxadustat: 1.6% vs. placebo: 3.3%); however, statistical values were not reported.[42] In Akizawa 2019, no patients required IV iron supplementation.[43] Further, Besarab 2015 reported a numerical reduction in the use of ESA treatment with roxadustat compared with placebo (pooled roxadustat: 9.1% vs. placebo: 17.9%), though statistical values were not reported.[41]

Hospitalization

In ALPS, the number of days of hospitalization per patient exposure year (PEY) was numerically reduced with roxadustat compared to placebo (26.5 days per PEY vs. 31.9 days per PEY); however, statistical values were not reported.[20]

Kidney Failure (ESKD)

Only ALPS reported the impact of roxadustat on progression to kidney failure as assessed by the composite of kidney failure, defined by the need for chronic dialysis or renal transplantation, doubling of serum creatinine, or death. In ALPS, there was no significant difference in the time to progression to kidney failure at two years with roxadustat compared to placebo (HR: 1.00; 95% CI: 0.76 to 1.30).[23]

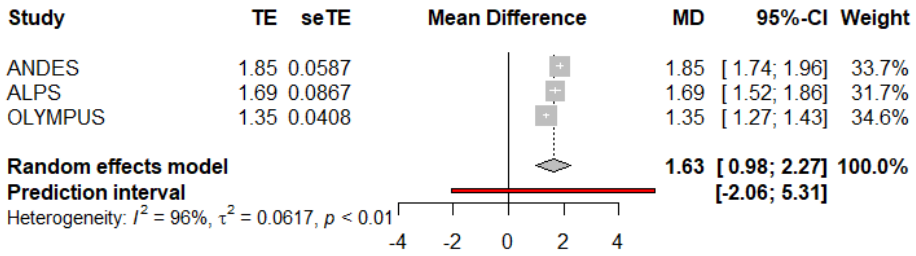
In ALPS, there was no significant difference in the annual rate of mean CFB in eGFR (LSM difference: 0.59 mL/min/1.73 m^2; 95%: -0.57 to 1.75).[20] In ANDES, there was no significant difference in the rate of change in eGFR over time, and the fixed-sequence testing was stopped. However, numerical values and the timeframe were not reported.[18] In OLYMPUS, the annual rate of mean CFB in eGFR prior to the initiation of dialysis or kidney transplant was significantly worse with roxadustat compared to placebo (LSM difference -0.51 mL/min/1.73 m^2; 95% CI: -1.00 to -0.01).[19] In contrast, in a post hoc subgroup analysis of ALPS, ANDES, and OLYMPUS, the one-year decline in eGFR was significantly better with roxadustat compared to placebo in patients who had a baseline eGFR of ≥15 mL/min/1.73 m^2 (LSM difference: 1.62 mL/min/1.73 m^2; $p<0.0001$).[17] This reduction is not likely to be clinically meaningful. The FDA accepts a doubling of serum creatinine level (corresponding to a change in eGFR of -57% or greater) as a surrogate outcome for kidney failure risk because it reflects a substantial decrease in kidney function and predicts the development of kidney failure.[96]

Anemia

DOLOMITES RCT (roxadustat vs. darbepoetin alfa): Mean CFB in Hb averaged over weeks 28 to 36 was not significantly different with roxadustat compared to darbepoetin alfa (LSM difference: 0.02 g/dL; 95% CI: -0.13 to 0.16).[21]

ALPS, ANDES, and OLYMPUS RCTs (roxadustat vs. placebo): Figure D9 shows the meta-analysis results on the primary outcome of mean CFB in Hb averaged over weeks 28 to 52 in ALPS, ANDES, and OLYMPUS.[22] The summary estimate is 1.63 g/dL (95% CI: 0.98 to 2.27) and suggests that roxadustat significantly increased Hb compared to placebo. However, statistical heterogeneity was significant (I^2=96%; $p<0.01$). A source of heterogeneity may be the small number of RCTs included in the meta-analysis.

Figure D9. Meta-Analysis of Hb in ALPS, ANDES, and OLYMPUS



95% CI: 95% confidence interval, I^2: I-squared, MD: mean difference, seTE: standard error, τ^2: between-study-variance estimator, TE: effect size

The 1517-CL-0310 RCT reported no significant difference in mean CFB in Hb averaged over weeks 18 to 24 with roxadustat compared to darbepoetin alfa (difference: -0.07 g/dL; 95% CI: -0.23 to 0.10).[38] Chen 2019, Besarab 2015, Chen 2017, and Akizawa 2019 also demonstrated that roxadustat significantly increased Hb compared to placebo at earlier timepoints (see Evidence Table 8 and Evidence Table 9).[40-43]

Measures of Inflammation and Iron Storage and Availability

The results for hepcidin and TSAT are described below, while the results for transferrin, soluble transferrin receptor, iron, total iron-binding capacity, and ferritin are presented in Evidence Table 5, Evidence Table 8, and Evidence Table 9.

Hepcidin

DOLOMITES RCT (roxadustat vs. darbepoetin alfa): At the time of this report, data regarding hepcidin for DOLOMITES are unavailable.

ALPS, ANDES, and OLYMPUS RCTs (roxadustat vs. placebo): In ALPS, mean hepcidin at week 104 was reduced with roxadustat compared to placebo (-10.05 ng/mL ± 33.67 vs. -7.44 ng/mL ± 22.92, respectively), though statistical values were not reported.[23] In ANDES, mean CFB in hepcidin at week 44 was significantly reduced with roxadustat compared to placebo (LSM difference: -25.71 ng/mL ± 6.53; 95% CI: -38.52 to -12.90).[18] In OLYMPUS, mean CFB in hepcidin at week 24 was significantly reduced with roxadustat compared to placebo (LSM difference: -45.36 ng/ml; p<0.001).[19] In a pooled analysis of ANDES, ALPS, and OLYMPUS, there was a significant reduction in mean CFB in hepcidin at week 24 with roxadustat compared to placebo (-23.05 ng/mL ± 86.03 vs. 12.33 ng/mL ± 87.77, respectively; p<0.0001).[97]

Results from other RCTs followed a similar trend. Chen 2019, Besarab 2015, Chen 2017, and Akizawa 2019 also demonstrated significantly reduced hepcidin with roxadustat compared to placebo at earlier timepoints (see Evidence Table 8 and Evidence Table 9).[40-43]

The clinical significance of the reductions in hepcidin is uncertain.

TSAT

DOLOMITES RCT (roxadustat vs. darbepoetin alfa): At the time of this report, data regarding TSAT for DOLOMITES are unavailable.

ALPS, ANDES, and OLYMPUS RCTs (roxadustat vs. placebo): In ALPS, mean TSAT at 104 weeks was reduced with roxadustat compared to placebo (-0.4% vs. 0.0%, respectively), though statistical values were not reported.[23] ANDES reported no significant difference in TSAT with roxadustat compared to placebo at 44 weeks (LSM difference: -0.12%; p=0.8984).[18] In OLYMPUS, there was no significant difference in mean CFB in TSAT from week 24 to end of treatment with roxadustat compared to placebo (LSM difference: -0.57%; p = 0.134).[19] In a pooled analysis of ANDES, ALPS, and OLYMPUS, TSAT was numerically reduced with roxadustat compared to epoetin alfa averaged over weeks 12 to 28 (-1.15% ± 11.82 vs. 0.38% ± 10.69, respectively); however, statistical values were not reported.[97]

Results from other RCTs are conflicting. Chen 2019 reported a significant reduction in TSAT with roxadustat compared to placebo at week nine (LSM difference: -4.3%; 95% CI: -7.4 to -1.1); however, during the open-label phase, TSAT increased to 22.1% at week 27.[40] Besarab 2015[41] and Chen 2017[42] demonstrated significant reductions in TSAT with roxadustat compared to placebo at end of treatment (26 or 29 days) and eight weeks, respectively (see Evidence Table 8 and Evidence Table 9), while Akizawa 2019[43] reported no significant difference with a pooled roxadustat estimate compared to placebo at the end of treatment (up to 24 weeks). However, low-dose roxadustat reached statistical significance compared to placebo (see Evidence Table 9).

Lipids

LDL-Cholesterol

DOLOMITES RCT (roxadustat vs. darbepoetin alfa): Mean CFB in LDL-cholesterol averaged over weeks 28 to 36 was significantly reduced with roxadustat compared to darbepoetin alfa (LSM difference: -15.58 mg/dL; 95% CI: -19.72 to -11.45).[21]

ALPS, ANDES, and OLYMPUS RCTs (roxadustat vs. placebo): ALPS and ANDES reported significant reductions in mean CFB in LDL-cholesterol averaged over weeks 12 to 28 with roxadustat compared to placebo, while OLYMPUS reported a significant reduction in mean CFB in LDL-cholesterol at 24 weeks with roxadustat compared to placebo (see Evidence Table 5).[18-20,22] In a pooled analysis of ALPS, ANDES, and OLYMPUS, mean CFB in LDL-cholesterol averaged over weeks 12 to 28 was significantly reduced with roxadustat compared to placebo (LSM difference: -19.83 mg/dL; 95% CI: -22.16 to -17.51).[98]

Similarly, Chen 2019, Chen 2017, and Akizawa 2019 reported significantly reduced LDL-cholesterol with roxadustat compared to placebo at earlier timepoints (see Evidence Table 8 and Evidence Table 9).[40,42,43]

However, the clinical significance of these reductions in LDL-cholesterol is uncertain.

HDL-Cholesterol

DOLOMITES RCT (roxadustat vs. darbepoetin alfa): At the time of this report, data regarding high-density lipoprotein (HDL)-cholesterol for DOLOMITES are unavailable.

ALPS, ANDES, and OLYMPUS RCTs (roxadustat vs. placebo): In ALPS, mean CFB in HDL-cholesterol at 104 weeks was reduced with roxadustat compared to placebo (-4.02 mg/dL ± 10.17 vs. 1.66 mg/dL ± 10.05); however, statistical values were not reported.[20] In a pooled analysis of ALPS, ANDES, and OLYMPUS, mean CFB in HDL-cholesterol averaged over weeks 12 to 28 was significantly reduced with roxadustat compared to placebo (LSM difference: -4.14 mg/dL ± 0.41).[98]

Chen 2017 reported a significant reduction in HDL-cholesterol at an earlier timepoint with roxadustat compared to placebo (see Evidence Table 9).[42]

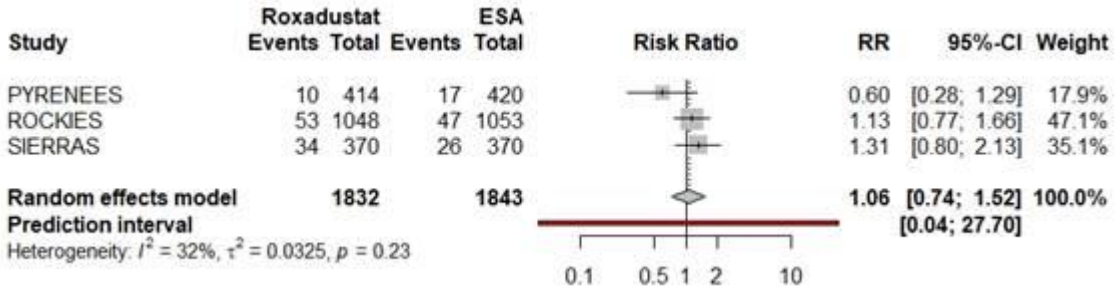
However, the clinical significance of these reductions in HDL-cholesterol is uncertain.

DD-CKD

Cardiovascular Safety

As described previously, the key RCTs (HIMALAYAS, PYRENEES, ROCKIES, and SIERRAS) were designed with Hb as the primary endpoint; thus, the number of cardiovascular events was low (see Evidence Table 26). Further, at the time of this report, no key RCTs reported adjudicated cardiovascular events. While MI was not reported for HIMALAYAS, we performed a meta-analysis of MI reported for PYRENEES, ROCKIES, and SIERRAS.[22,25,99,100] As seen in Figure D10, the meta-analysis results suggest that the risk of MI is not significantly different with roxadustat compared to ESAs (RR: 1.06; 95% CI: 0.74 to 1.52; I^2=32%).

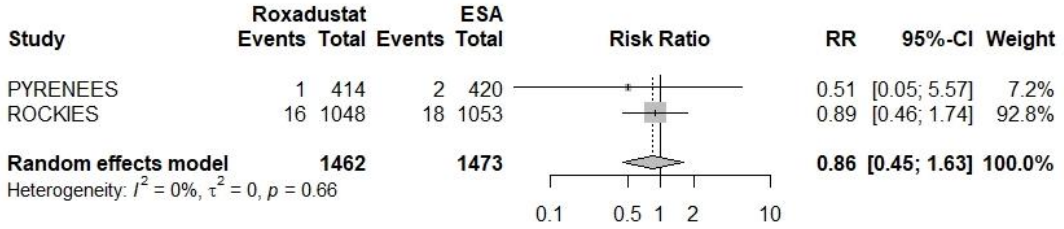
Figure D10. Meta-Analysis of MI in PYRENEES, ROCKIES, and SIERRAS



95% CI: 95% confidence interval, ESA: erythropoiesis-stimulating agent, I^2: I-squared, RR: risk ratio, τ^2: between-study-variance estimator

We also performed a meta-analysis of stroke reported for PYRENEES and ROCKIES.[25,99,100] As seen in Figure D11, the meta-analysis results suggest that the risk of stroke is not significantly different with roxadustat compared to ESAs (RR: 0.86; 95% CI: 0.45 to 1.63; I^2=0%).

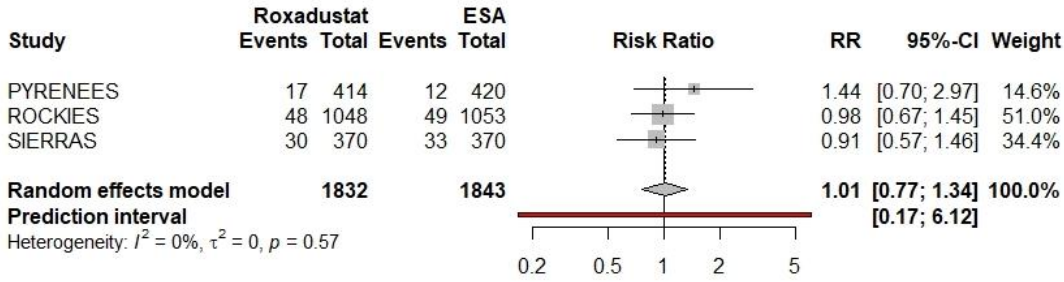
Figure D11. Meta-Analysis of Stroke in PYRENEES and ROCKIES



95% CI: 95% confidence interval, ESA: erythropoiesis-stimulating agent, I^2: I-squared, RR: risk ratio, τ^2: between-study-variance estimator

We performed a meta-analysis of heart failure reported for PYRENEES, ROCKIES, and SIERRAS.[22,25,99,100] As seen in Figure D12, the meta-analysis results suggest that the risk of heart failure is not significantly different with roxadustat compared to ESAs (RR: 1.01; 95% CI: 0.77 to 1.34; I^2=0%).

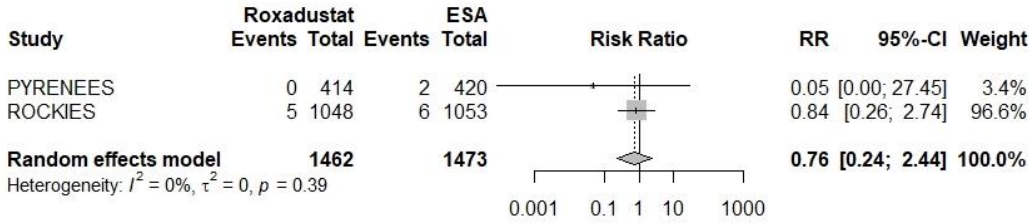
Figure D12. Meta-Analysis of Heart Failure in PYRENEES, ROCKIES, and SIERRAS



95% CI: 95% confidence interval, ESA: erythropoiesis-stimulating agent, I^2: I-squared, RR: risk ratio, τ^2: between-study-variance estimator

Finally, we performed a meta-analysis of unstable angina reported for PYRENEES and ROCKIES.[25,99,100] As seen in Figure D13, the meta-analysis results suggest that the risk of unstable angina is not significantly different with roxadustat compared to ESAs (RR: 0.76; 95% CI: 0.24 to 2.44; I^2=0%).

Figure D13. Meta-Analysis of Unstable Angina in PYRENEES and ROCKIES



95% CI: 95% confidence interval, ESA: erythropoiesis-stimulating agent, I^2: I-squared, RR: risk ratio, τ^2: between-study-variance estimator

A pooled on-treatment analysis of HIMALAYAS, ROCKIES, and SIERRAS reported that roxadustat was not significantly different from epoetin alfa in the risk of MACE (HR: 0.96; 95% CI: 0.82 to 1.13) and all-cause mortality (HR: 0.96; 95% CI: 0.79 to 1.17) in the first 52 weeks.[17] However, the risk of MACE+ was significantly reduced with roxadustat compared to epoetin alfa (HR: 0.86; 95% CI: 0.74 to 0.98).[17] The incidence of the MACE+ components is shown in Table D9. As seen in Table D9, the difference reported between the MACE and MACE+ results is due to the inclusion of reductions in unstable angina requiring hospitalization and congestive heart failure requiring hospitalization.

Table D9. Incidence of MACE+ Components in Pooled Analysis of HIMALAYAS, ROCKIES, and SIERRAS

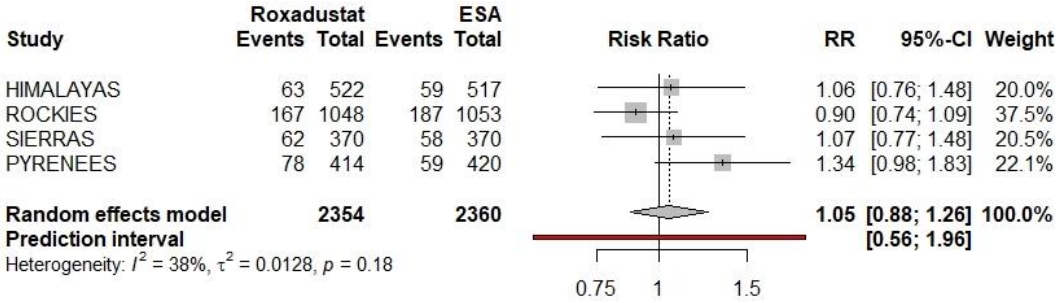
Outcome	Number of Events (%)		RR (95% CI)
	Roxadustat (N=1940)	Epoetin Alfa (N=1940)	
All-Cause Mortality	207 (10.7)	232 (12.0)	0.89 (0.75. 1.06)
MI	103 (5.3)	109 (5.6)	0.95 (0.73, 1.23)
Stroke	45 (2.3)	50 (2.6)	0.90 (0.60, 1.34)
Unstable Angina Requiring Hospitalization	18 (0.9)	22 (1.1)	0.82 (0.44, 1.52)
Congestive Heart Failure Requiring Hospitalization	120 (6.2)	166 (8.6)	0.72 (0.58, 0.91)

95 CI: 95% confidence interval, MI: myocardial infarction, N: total number, RR: risk ratio

Importantly, the pooled analysis did not include the fourth key RCT (PYRENEES). Thus, we performed a meta-analysis of all-cause mortality reported for HIMALAYAS, PYRENEES, ROCKIES, and SIERRAS.[22] As seen in Figure D14, the meta-analysis results demonstrate that the risk of all-cause mortality is not significantly different with roxadustat compared to ESAs (RR: 1.05; 95% CI: 0.88 to

1.26; I^2=38%). However, the summary estimate is higher than was reported in the pooled analysis, likely due to PYRENEES's inclusion.

Figure D14. Meta-Analysis of All-Cause Mortality in HIMALAYAS, PYRENEES, ROCKIES, and SIERRAS



95% CI: 95% confidence interval, ESA: erythropoiesis-stimulating agent, I^2: I-squared, N: total number, No: number, RR: risk ratio

Importantly, these results should be interpreted with caution as the timepoints in which cardiovascular safety events were reported in the key RCTs are unclear at the time of this report.

Other RCTs with shorter durations were not powered to detect significant differences in cardiovascular safety events and reported low event rates (see Evidence Table 27 and Evidence Table 28).

HRQoL

PYRENEES assessed HRQoL with SF-36, EQ-5D-5L, Fact-An, and PGIC.[25,99] Higher scores on SF-36, EQ-5D-5L, and Fact-An indicate better quality of life. In the PGIC, patients rate their change as "very much improved," "much improved," "minimally improved," "no change," "minimally worse," "much worse," or "very much worse."

SF-36

There was no significant difference in mean CFB in SF-36 PF sub-score averaged over weeks 12 to 28 with roxadustat compared to ESAs (LSM difference: 0.21; 95% CI: -0.65 to 1.06). There was also no significant difference in mean CFB in SF-36 VT sub-score averaged over weeks 12 to 28 with roxadustat compared to ESAs (LSM difference: 0.86; 95% CI: -0.12 to 1.83). Further, mean CFB in SF-36 Physical Component score was not significantly different between the groups (LSM difference: 0.52; 95% CI: -0.21 to 1.25). Importantly, a MCID of 3 to 5 points was not reached in these assessments.[47]

EQ-5D-5L VAS

Mean CFB in EQ-5D-5L VAS score averaged over weeks 12 to 28 was numerically greater with roxadustat compared to ESAs (3.04 ± 14.91 vs. 2.74 ± 14.78, respectively), though statistical values were not reported. While a MCID for EQ-5D-5L VAS score has not been established in patients with CKD, in stroke patients undergoing rehabilitation,[91] oncology patients,[92] and patients with COPD,[93] a MCID ranged from 8 to 12 points.

FACT-An

There was no significant difference in mean CFB in Total FACT-An score averaged over weeks 12 to 28 with roxadustat compared to ESAs (LSM difference: -0.11; 95% CI: -2.67 to 2.46). There was also no significant difference in mean CFB in FACT-An AnS averaged over weeks 12 to 28 with roxadustat compared to ESAs (LSM difference: 0.17; 95% CI: -1.08 to 1.43). Importantly, MCIDs of 6 points and 4 points for Total FACT-An and FACT-An AnS, respectively, were not reached.[94]

PGIC

The proportion of patients who rated their status as "very much improved," "much improved," and "minimally improved" was numerically greater with roxadustat compared to ESAs at week 104 (61.6% vs. 51.3%, respectively), though statistical values were not reported.

Rescue Therapy

There was no significant difference in the risk of rescue therapy to end of treatment (up to week 104) with roxadustat compared to ESAs (see Table D10) in PYRENEES.[22,25,99] Similarly, in ROCKIES, there was no significant difference in the risk of rescue therapy in the first 52 weeks with roxadustat compared to epoetin alfa (see Table D10).[22,26,100]

The risk of blood transfusion was significantly reduced with roxadustat compared to epoetin alfa for ROCKIES at the end of study and SIERRAS in the first 52 weeks (see Table D10).[22,26,99] In PYRENEES and HIMALAYAS, there were no significant differences in this endpoint with roxadustat compared to ESAs and epoetin alfa, respectively (see Table D10).[25,95] However, a pooled analysis of HIMALAYAS, ROCKIES, and SIERRAS reported a significant reduction in this endpoint with roxadustat compared to epoetin alfa during treatment (HR: 0.82; 95% CI: 0.679 to 0.997).[95]

Table D10. Rescue Therapy in HIMALAYAS, PYRENEES, ROCKIES, and SIERRAS

		HIMALAYAS		PYRENEES		ROCKIES		SIERRAS	
		Roxadustat (N=522)	Epoetin Alfa (N=513)	Roxadustat (N=413)	ESAs (N=420)	Roxadustat (N=1048)	Epoetin Alfa (N=1053)	Roxadustat (N=370)	Epoetin Alfa (N=371)
Risk of Rescue Therapy, HR (95% CI)		NR		0.98 (0.66, 1.46)*		0.83 (0.64, 1.07)†		NR	
Risk of Blood Transfusion, HR (95% CI)		1.26 (0.64, 1.07)‡		0.87 (0.57, 1.31)*		0.26 (0.17, 0.41)†		0.67 (0.47, 0.97)†	
Monthly IV Iron Suppl., mg	**Mean (SD)**	46.90 (8.10)¶	71.50 (7.50)¶	12.00 (47.60)#	44.80 (88.60)#	58.70 (236.1)§§	91.40 (225.6)§§	17.10 (53.40)¶¶	37.00 ± 106.80¶¶
	LSM Diff. (95% CI); p-value	NR; p=0.0002		-48.70 (-70.30, -27.00); p<0.001		NR; p<0.001		NR; p=0.00091	

95% CI: 95% confidence interval, ESAs: erythropoiesis-stimulating agents, HR: hazard ratio, IV: intravenous, LSM: least squares mean, mg: milligram, N: total number, NR: not reported

*At end of treatment (up to week 104).

†In the first 52 weeks.

‡During treatment.

§At end of study.

¶At week 45 to 52.

#At week 53 to 104.

§§At week 35 to end of study.

¶¶Time period unclear.

HIMALAYAS, PYRENEES, ROCKIES, and SIERRAS reported a significant reduction in mean monthly IV iron use at week 45 to 52, week 53 to 104, and week 36 to end of study, respectively, though the time period for SIERRAS is unclear at the time of this report (see Table D10).[22,24-26,99,100] Further, in PYRENEES, the risk of IV iron to end of treatment (up to 104 weeks) was significantly reduced with roxadustat compared to ESAs (HR: 0.37; 95% CI: 0.29 to 0.47).[22,25]

Chen 2019 reported no significant difference in the use of rescue therapy with roxadustat compared to epoetin alfa (HR: 1.68; 95% CI: 0.18 to 16.19).[40] In Chen 2017, no patients required rescue therapy (see Evidence Table 22).[42] Provenzano 2016 reported a numerical reduction in the use of IV iron with roxadustat compared to epoetin alfa, though statistical values were not reported (see Evidence Table 23).[45]

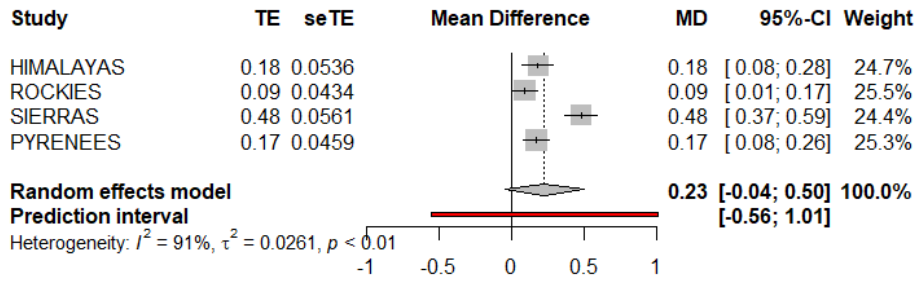
Hospitalization

In PYRENEES, the mean number of hospitalizations (included all non-HD hospitalizations) at the end of treatment (up to week 104) was comparable with roxadustat compared to ESAs (0.9 ± 1.3 vs. 0.9 ± 1.5, respectively); however, statistical values were not reported.[99] The mean number of days of hospitalization at the end of treatment (up to week 104) was numerically greater with roxadustat compared to ESAs (12.19 days ± 34.12 vs. 7.87 days ± 22.95, respectively), though statistical values were not reported.[99] Further, the risk of hospitalization at end of treatment (up to week 104) was not significantly different with roxadustat compared to ESAs (HR: 1.55; 95% CI: 0.94 to 1.41).[99]

Anemia

Figure D15 shows the meta-analysis results on the primary outcome of mean CFB in Hb averaged over weeks 28 to 52 in HIMALAYAS, PYRENEES, ROCKIES, and SIERRAS.[22,24-26] Though the individual key RCTs each reported a significant increase in Hb with roxadustat compared to ESAs, as seen in Figure D14, the summary estimate of our meta-analysis was 0.23 g/dL (95% CI: -0.04 to 0.50) with a wide confidence interval and high heterogeneity (I^2=91%; p<0.01). Sources of heterogeneity may be differences in baseline Hb and the small number of RCTs included in the meta-analysis.

Figure D15. Meta-Analysis of Hb in HIMALAYAS, PYRENEES, ROCKIES, and SIERRAS



95% CI: 95% confidence interval, I^2: I-squared, MD: mean difference, seTE: standard error, τ^2: between-study-variance estimator, TE: effect size

Chen 2019, Akizawa 2020, Provenzano 2016, Chen 2017, and the 1517-CL-0304 RCT also demonstrated that roxadustat does not significantly increase Hb compared to darbepoetin alfa and epoetin alfa at earlier timepoints (see Evidence Table 22 and Evidence Table 23).[40,42,44-46]

Measures of Inflammation and Iron Storage and Availability

The results for hepcidin and TSAT are presented below, while the results for transferrin, soluble transferrin receptor, iron, total iron-binding capacity, and ferritin are presented in Evidence Table 21, Evidence Table 22, and Evidence Table 23.

Hepcidin

In PYRENEES, hepcidin was numerically reduced at the end of study (up to 108 weeks) with roxadustat compared to ESAs (-27.19 ng/mL ± 52.17 vs. -17.67 ng/mL ± 51.69, respectively), though statistical values were not reported.[22,25,99] In ROCKIES, mean CFB in hepcidin at week 24 was significantly reduced with roxadustat compared to epoetin alfa (-44.99 ng/mL vs. -16.77 ng/mL, respectively; p<0.001).[26] In contrast, in SIERRAS, there was no significant difference in mean CFB in hepcidin with roxadustat compared to epoetin alfa at 52 weeks (-95.53 ng/mL ± 148.27 vs. -66.66 ng/mL ± 141.61, respectively; p=0.06).[26] In a pooled analysis of HIMALAYAS, ROCKIES, and SIERRAS, hepcidin was significantly reduced with roxadustat compared to epoetin alfa at 24 weeks (-60.35 ng/mL ± 134.55 vs. -34.08 ng/mL ± 137.37, respectively; p<0.0001).[101]

Results from other RCTs demonstrate a trend towards reduced hepcidin with roxadustat compared to ESAs. Chen 2019 and Akizawa 2020 reported numerically reduced hepcidin with roxadustat compared to epoetin alfa and darbepoetin alfa, respectively, at 27 weeks and end of treatment (up to 24 weeks), though statistical analyses were not reported.[40,44] Provenzano 2016 reported significantly reduced hepcidin with roxadustat compared to epoetin alfa at 19 weeks but not six weeks (see Evidence Table 22 and Evidence Table 23).[45] Further, Chen 2017 reported significantly

reduced hepcidin with a high-starting dose of roxadustat compared to epoetin alfa but not low, medium, or pooled roxadustat (see Evidence Table 23).[42]

Importantly, the clinical significance of the reported changes in hepcidin is uncertain.

TSAT

In PYRENEES, TSAT was numerically reduced at end of study (up to week 108) with roxadustat compared to ESAs (-5.47% ± 16.63 vs. -3.76% ± 17.81%, respectively), though statistical values were not reported.[22,25,99] In SIERRAS, the reduction in TSAT at week 52 was significantly smaller with roxadustat compared to epoetin alfa (-7.96% ± 13.70 vs. -9.78% ± 13.07, respectively; p=0.0341).[22] ROCKIES reported no significant difference in TSAT between week 24 and end of treatment with roxadustat compared to epoetin alfa (-1.92% vs. -2.44%, respectively; p=0.287).[22,26] HIMALAYAS reported numerically similar mean CFB in TSAT with roxadustat compared to epoetin alfa at 52 weeks (-2.10% ± 0.7 vs. -2.90% ± 0.5, respectively); however, these results should be interpreted with caution as they were obtained through digitization and statistical values were not reported.[22,24] In a pooled analysis of HIMALAYAS, ROCKIES, and SIERRAS, mean CFB in TSAT was numerically greater with roxadustat compared to epoetin alfa at week 20 (-1.70% ± 13.70 vs. -2.70% ± 12.43, respectively); however, statistical values were not reported.[101]

Results from other RCTs suggest that roxadustat does not consistently lead to increased TSAT compared to ESAs, particularly at earlier timepoints. Chen 2019 reported a significantly smaller decrease in TSAT with roxadustat compared to epoetin alfa at 27 weeks (LSM difference: 4.2% ± 1.4; 95% CI: 1.5 to 6.9).[40] Akizawa 2020 also reported numerically similar findings, though statistical values were not reported (see Evidence Table 22).[44] In contrast, Provenzano 2016 reported no significant differences in TSAT with roxadustat compared epoetin alfa at six and 19 weeks, while Chen 2017 reported no significant differences in this outcome at six weeks (see Evidence Table 23).[42,45]

Lipids

LDL-Cholesterol

PYRENEES reported a significant reduction in mean CFB in LDL-cholesterol averaged over weeks 12 to 28 with roxadustat compared to ESAs (LSM difference: -14.70 mg/dL; 95% CI: -0.45 to -0.31).[22,25] Further, SIERRAS also reported a significant reduction in mean CFB in LDL-cholesterol averaged over weeks 12 to 28 with roxadustat compared to epoetin alfa (LSM difference: -14.67 mg/dL; 95% CI: -17.62 to -11.70).[22] ROCKIES reported a significant reduction in mean CFB in LDL-cholesterol at week 24 (LSM difference: -12.76 mg/dL; 95% CI: -0.39 to -0.27).[22,26] Further, a pooled analysis of HIMALAYAS, ROCKIES, and SIERRAS reported a significant reduction in LDL-cholesterol averaged

over weeks 12 to 28 with roxadustat compared to epoetin alfa (LSM difference: -15.80 mg/dL; 95% CI: -17.54 to -14.06).[98]

Chen 2019 and Chen 2017 also reported significant reductions in LDL-cholesterol at earlier timepoints (see Evidence Table 22 and Evidence Table 23).[40,42]

However, the clinical significance of these reductions in LDL-cholesterol is uncertain.

HDL-Cholesterol

A pooled analysis of HIMALAYAS, ROCKIES, and SIERRAS reported a significant reduction in HDL-cholesterol averaged over weeks 12 to 28 with roxadustat compared to epoetin alfa (LSM difference: -8.99 mg/dL ± 2.82; p<0.0001).[98]

Chen 2019 and Chen 2017 reported significant reductions in HDL-cholesterol at earlier timepoints with roxadustat compared to epoetin alfa (see Evidence Table 22 and Evidence Table 23).[40,42]

However, the clinical significance of these reductions in HDL-cholesterol is uncertain.

Harms

Importantly, the current package insert for roxadustat in Japan warns that roxadustat may cause serious thromboembolism, including cerebral infarction, MI, and pulmonary embolism, with a possible fatal outcome.[51] Cardiovascular safety events in the key RCTs are discussed above for DI- and DD-CKD populations.

DI-CKD

DOLOMITES RCT (roxadustat vs. darbepoetin alfa): Most TEAEs were of mild-to-moderate severity (see Evidence Table 14).[21] The most commonly reported TEAEs included kidney failure, hypertension, decrease in eGFR, and peripheral edema. As seen in Table D11, the incidence of any TEAE was marginally lower with roxadustat compared to darbepoetin alfa (91.6% vs. 92.5%, respectively), while the incidence of serious TEAEs was higher with roxadustat (64.7% vs. 61.8%, respectively). Further, the incidence of discontinuation due to TEAEs was higher with roxadustat compared to darbepoetin alfa (7.7% vs. 3.8%, respectively). Serious AEs reported included all-cause mortality and cardiovascular events, which are presented above.

Table D11. AEs in DOLOMITES, ALPS, ANDES, and OLYMPUS

	DOLOMITES		ALPS		ANDES		OLYMPUS	
	ROX (N=323)	DA (N=293)	ROX (N=391)	PBO (N=203)	ROX N=611)	PBO (N=305)	ROX (N=1384)	PBO (N=1377)
Any TEAEs, n (%)	296 (91.6)	271 (92.5)	343 (87.7)	176 (86.7)	564 (92.3)	273 (89.5)	NR	NR
Serious TEAEs, n (%)	209 (64.7)	181 (61.8)	241 (61.6)	115 (56.7)	ERP100PY: 74.2	ERP100PY: 66	NR	NR
D/C due to AEs, n (%)	25 (7.7)*	11 (3.8)*	23 (5.9)*	8 (3.9)*	85 (13.8)†	30 (9.8)†	79 (5.7)	52 (3.8)

DA: darbepoetin alfa, ERP100PY: event rate per 100 person years, D/C: discontinuation, N: total number, NR: not reported, PBO: placebo, ROX: roxadustat, TEAE: treatment-emergent adverse event

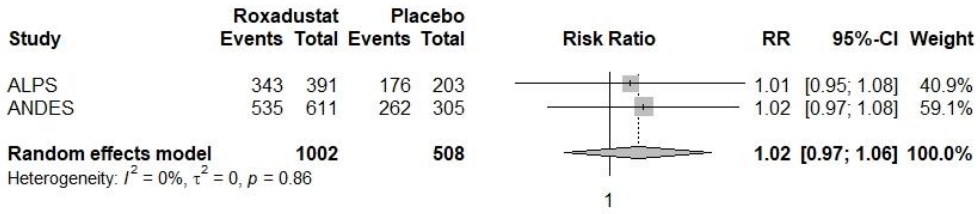
*Due to TEAEs.

†Due to AEs or death.

ALPS, ANDES, and OLYMPUS RCTs (roxadustat vs. placebo): Most TEAEs in the key RCTs were of mild-to-moderate severity (see Evidence Table 14).[22,24,39] The most commonly reported TEAEs included ESKD, decrease in eGFR, nausea, hyperkalemia, and hypertension. The time to first exacerbation of hypertension (systolic blood pressure [SBP] ≥170 mmHg or diastolic blood pressure [DBP] ≥110 mmHg and an increase from baseline ≥20 mmHg [SBP] or ≥15 mmHg [DBP]) was not significantly different with roxadustat compared to placebo (HR: 1.12; 95% CI: 0.95 to 1.32).[102]

We conducted a meta-analysis of any TEAE for ALPS and ANDES.[18,20,22] As seen in Figure D16, there were no significant differences in the risk of any TEAE (RR: 1.02 95% CI: 0.97 to 1.06; I^2=0%) with roxadustat compared to placebo.

Figure D16. Meta-Analysis of Any TEAE in ALPS and ANDES

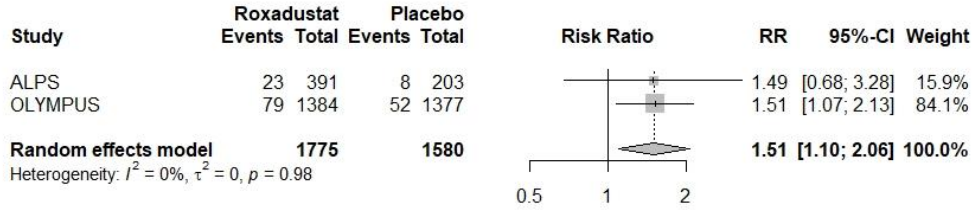


95% CI: 95% confidence interval, I^2: I-squared, RR: risk ratio

The incidence of serious TEAEs was higher with roxadustat compared to placebo in ALPS (61.6% vs. 56.7%, respectively) and ANDES (event rate per 100 person years: 74.2 vs. 66.0 respectively).[18,20,40]

We also conducted a meta-analysis of discontinuation due to AEs for ALPS and OLYMPUS.[19,22] As seen in Figure D17, the risk of discontinuation due to AEs was significantly greater with roxadustat compared to placebo (RR: 1.51; 95% CI: 1.10 to 2.06; I^2=0%).

Figure D17. Meta-Analysis of Discontinuation Due to AEs in ALPS and OLYMPUS



95% CI: 95% confidence interval, AE: adverse event, D/C: discontinuation, I2: I-squared, N: number: No.: number, RR: risk ratio, τ2: between-study-variance estimator

Serious AEs reported included all-cause mortality and cardiovascular events, which are presented above.

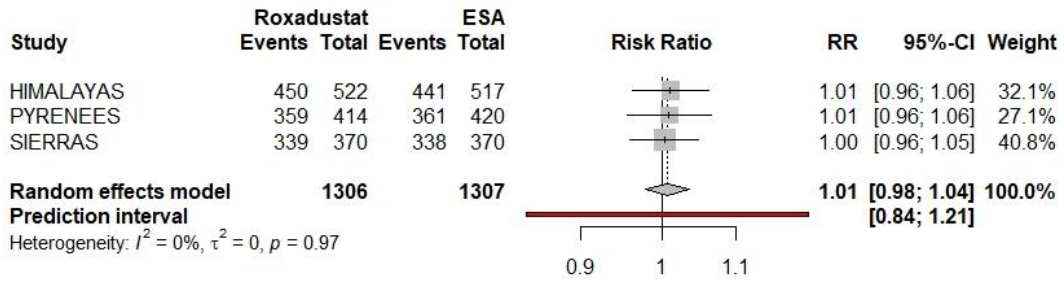
Other RCTs reported similar findings (see Evidence Table 15 and Evidence Table 16).[40-43]

DD-CKD

Most TEAEs in the key RCTs of roxadustat were of mild-to-moderate severity (see Evidence Table 29).[22,24-26] The most commonly reported TEAEs included nausea, diarrhea, hyperkalemia, and hypertension. In a pooled analysis of HIMALAYAS, ROCKIES, and SIERRAS, the time to first exacerbation of hypertension (SBP ≥170 mmHg or DBP ≥110 mmHg and an increase from baseline ≥20 mmHg [SBP] or ≥15 mmHg [DBP]) was not significantly different with roxadustat compared to epoetin alfa (HR: 1.06; 95% CI: 0.93 to 1.21).[102]

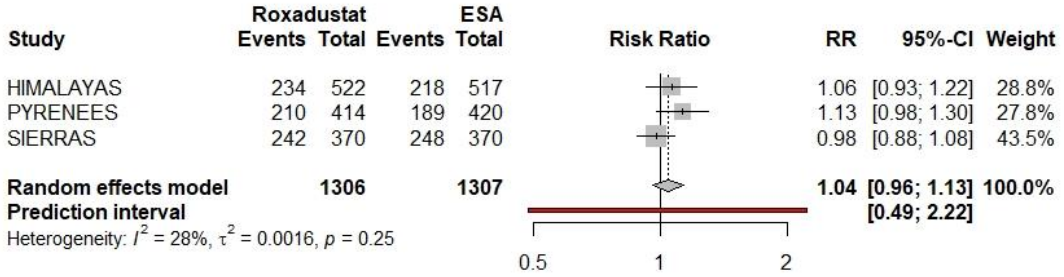
We conducted meta-analyses of any TEAE and serious TEAEs for HIMALAYAS, PYRENEES, and SIERRAS and a meta-analysis of discontinuation due to AEs for HIMALAYAS, PYRENEES, and ROCKIES.[22,24-26] As seen in Figures D18 and D19, there were no significant differences in the risk of any TEAE (RR: 1.01; 95% CI: 0.98 to 1.04; I^2=0%) or serious TEAE (RR: 1.04; 95% CI: 0.96 to 1.13; I^2=28%) with roxadustat compared to ESAs.

Figure D18. Meta-Analysis of Any TEAE in HIMALAYAS, PYRENEES, and SIERRAS



95% CI: 95% confidence interval, AE: adverse event, D/C: discontinuation, I^2: I-squared, N: number: No.: number, RR: risk ratio, τ^2: between-study-variance estimator

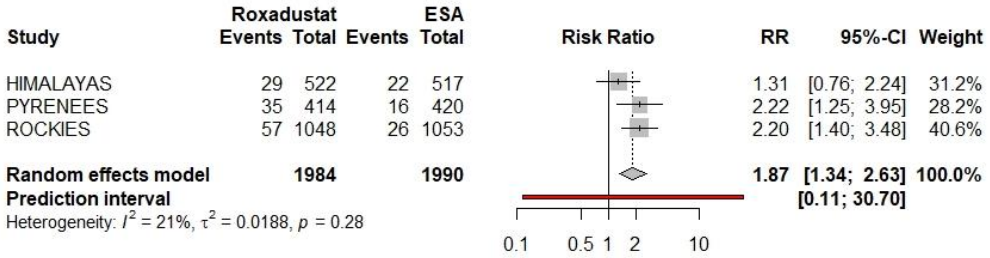
Figure D19. Meta-Analysis of Serious TEAEs in HIMALAYAS, PYRENEES, and SIERRAS



95% CI: 95% confidence interval, AE: adverse event, D/C: discontinuation, I^2: I-squared, N: number: No.: number, RR: risk ratio, τ^2: between-study-variance estimator

However, as seen in Figure D20, the risk of discontinuation due to adverse events was significantly greater with roxadustat compared to ESAs (RR: 1.87; 95% CI: 1.34 to 2.63; I^2=21%).

Figure D20. Meta-Analysis of Discontinuation Due to Adverse Events in HIMALAYAS, PYRENEES, and ROCKIES



95% CI: 95% confidence interval, AE: adverse event, D/C: discontinuation, I^2: I-squared, N: number: No.: number, RR: risk ratio, τ^2: between-study-variance estimator

Serious AEs reported included all-cause mortality and cardiovascular events, which are presented above.

Other RCTs reported similar findings (see Evidence Table 30 and Evidence Table 31).[40,42,44-46]

D3. Evidence Tables

Evidence Tables 1-40 begin on the following page.

Evidence Table 1. Study Design

Trial Name (NCT), Author	Study Design & Follow-Up Duration	Location	N	Arms	Key Inclusion Criteria	Key Exclusion Criteria	Definitions
ALPS **NCT01887600**[20]	Phase III, multicenter, double-blind, placebo-controlled, randomized trial Follow-Up: – Treatment period: 52 to 104 weeks – Post-treatment Follow-up period: 4 weeks	Global	597	**Roxadustat (N=394)** Weight-based starting doses: – ≥45 to ≤70 kg: 70 mg TIW – >70 to ≤160 kg: 100mg TIW **Placebo (N=203)**	– ≥18 years of age – CKD diagnosis (stage 3-5) not on dialysis – eGFR <60 mL/min/1.73 m^2 – Hb ≤10.0 g/dL – Ferritin ≥30 ng/mL – TSAT ≥5%	– ESA treatment within 12 weeks – >1 dose of IV iron within 12 weeks – Treatment with iron-chelating agents within 4 weeks – Blood transfusion within 8 weeks – NYHA Class III or IV congestive heart failure – MI, acute coronary syndrome, stroke, seizure, or a thrombotic/thromboembolic event within 12 weeks – Uncontrolled hypertension	**Hb Response:** Hb ≥11.0 g/dL and change ≥1.0 g/dL if baseline Hb >8.0 g/dL; or change ≥2.0 g/dL if baseline Hb ≤8.0 g/dL at 2 consecutive visits separated by at least 5 days during the first 24 weeks of treatment without rescue therapy
ANDES **NCT01750190**[18]	Phase III, multicenter, double-blind, placebo-controlled, randomized trial Follow-Up: – Treatment period: 52 to 156 weeks – Post-treatment Follow-up period: 4 weeks	Global	922	**Roxadustat (N=616)** Weight-based starting doses: – ≥45 to ≤70 kg: 70 mg TIW – >70 to ≤160 kg: 100mg TIW **Placebo (N=306)**	– ≥ 18 years of age – CKD diagnosis (stage 3-5) not on dialysis – eGFR <60 mL/min/1.73 m^2 – Hb ≤10.0 g/dL – Ferritin ≥30 ng/mL – TSAT ≥5%	– ESA treatment within 12 weeks – >1 dose of IV iron within 12 weeks – Blood transfusion within 8 weeks – Severe congestive heart failure, recent heart attack, stroke, seizure, or blood clot – Uncontrolled blood pressure – Renal cell carcinoma – History of malignancy	**Hb Response:** Hb ≥11.0 g/dL and change ≥1.0 g/dL if baseline Hb >8.0 g/dL; or change ≥2.0 g/dL if baseline Hb ≤8.0 g/dL at 2 consecutive visits separated by at least 5 days during the first 24 weeks of treatment without rescue therapy
DOLOMITES **NCT02021318**[21]	Phase III, multicenter, open-label, active-controlled, randomized trial	Europe	616	**Roxadustat (N=323)** Weight-based starting dose **Darbepoetin alfa (N=293)**	– ≥ 18 years of age – CKD (stage 3-5) not on dialysis – eGFR <60 ml/min/1.73 m^2 – Hb ≤10.5 g/dL	– ESA treatment within 12 weeks prior to randomization – Received any IV iron within 6 weeks prior to randomization	**Hb Response:** Hb ≥11.0 g/dL and change ≥1.0 g/dL if baseline Hb >8.0 g/dL; or change ≥2.0 g/dL if baseline Hb ≤8.0 g/dL at 2

Trial Name (NCT), Author	Study Design & Follow-Up Duration	Location	N	Arms	Key Inclusion Criteria	Key Exclusion Criteria	Definitions
	Follow-Up: – Treatment period: 104 weeks – Post-treatment Follow-up period: 4 weeks			Dosed according to European Summary of Product Characteristics	– Suitable for ESA treatment	– Treatment with iron-chelating agents within 4 weeks prior to randomization – Blood transfusion within 8 weeks prior to randomization – NYHA Class III or IV congestive heart failure – MI, acute coronary syndrome, stroke, seizure, or a thrombotic/thromboembolic event within 12 weeks prior to randomization – History of malignancy	consecutive visits separated by at least 5 days during the first 24 weeks of treatment without rescue therapy
OLYMPUS **NCT02174627**[19]	Phase III, double-blind, placebo controlled, randomized trial Follow-Up: – Treatment period: up to 4 years – Post-treatment Follow-up: 4 weeks	Global	2781	**Roxadustat (N=1,393)** – 70 mg TIW **Placebo (N=1,388)**	– ≥ 18 years of age – CKD (stage 3-5) not on dialysis – eGFR <60 mL/min/1.73 m^2 – Hb <10.0 g/dL – Ferritin ≥50 ng/mL – TSAT ≥15 %	– ESA treatment within 6 weeks prior to randomization – Blood transfusion during screening period – NYHA Class III or IV congestive heart failure – MI, acute coronary syndrome, stroke, seizure, or a thrombotic/thromboembolic event within 12 weeks – History of prostate cancer, breast cancer or any other malignancy	**Hb Response:** Hb ≥11.0 g/dL and change ≥1.0 g/dL if baseline Hb >8.0 g/dL; or change ≥2.0 g/dL if baseline Hb ≤8.0 g/dL at 2 consecutive visits separated by at least 5 days during the first 24 weeks of treatment without rescue therapy

Trial Name (NCT), Author	Study Design & Follow-Up Duration	Location	N	Arms	Key Inclusion Criteria	Key Exclusion Criteria	Definitions
FGCL-4592-808 **NCT02174627** **Chen 2019[40]**	Phase III, multicenter, double-blind, placebo controlled, randomized and open-label trial Follow-Up: – Randomized phase: 8 weeks – Open-label phase: 18 weeks	China	154	**Roxadustat (n=102)** Weight-based starting doses: – ≥40-<60 kg: 70 mg TIW – ≥60 kg: 100 mg TIW **Placebo (n=52)**	– 18 – 75 years of age – CKD (stage 3-5) not on dialysis – eGFR <60 mL/min/1.73 m^2 – Hb ≥7.0 g/dL and <10.0 g/dL – ALT and AST < 1.5x ULN – No ESA treatment ≥5 weeks prior to randomization	– IV iron supplementation during the screening period – Blood transfusion within 12 weeks prior to day 1 or anticipated need for transfusion – NYHA Class III or IV congestive heart failure – MI, acute coronary syndrome, stroke, seizure, or a thromboembolic event within 52 weeks – Systolic BP ≥160 mmHg or diastolic BP ≥95 mmHg within 2 weeks prior to randomization – History of malignancy	
1517-CL-0310 **NCT02988973[38]**	Phase III, randomized, open label, active-controlled trial Follow-Up: – Cohorts 1 and 3: 52 weeks – Cohort 2: 24 weeks	Japan	334	**Roxadustat (N=NR)** – Converted from rHuEPO or darbepoetin alfa (Cohort 1) – Converted from epoetin beta pegol (Cohort 3) **Darbepoetin alfa, (N=NR)** – Converted from rHuEPO or darbepoetin alfa (Cohort 2)	– CKD not on dialysis – Hb ≥10.0 g/dL and ≤12.0 g/dL – TSAT ≥20% or ferritin ≥100 ng/mL – Receiving ESA by SC injection and whose Hb values are considered stable	– Blood transfusion and/or a surgical procedure considered to promote anemia and/or ophthalmological surgery within 4 weeks – Concurrent congestive heart failure (NYHA Class III or higher) – History of hospitalization for treatment of stroke, myocardial infarction, or pulmonary embolism within 12 weeks – Uncontrolled hypertension – Previous or current malignant tumor (no recurrence for at least 5 years is eligible) – Concurrent untreated retinal neovascular lesion or macular edema	

Trial Name (NCT), Author	Study Design & Follow-Up Duration	Location	N	Arms	Key Inclusion Criteria	Key Exclusion Criteria	Definitions
FGCL-SM4592-017 **NCT00761657** **Besarab 2015**[41]	Phase IIa, single-blind, placebo-controlled, multicenter, dose-ranging trial Follow-Up: – Treatment period: 4 weeks – Post-Treatment Follow-up: 8 weeks	US	116	**Roxadustat (N=88)** – 0.7 mg/kg BIW – 0.7 mg/kg TIW – 1.0 mg/kg BIW – 1.0 mg/kg TIW – 1.5 mg/kg BIW – 1.5 mg/kg TIW – 2.0 mg/kg BIW – 2.0 mg/kg TIW **Placebo (N=28)**	– 18 – 80 years of age – CKD (stage 3 or 4) not on dialysis – eGFR ≥15-≤59 ml/min/1.73 m^2 – Hb < 11.0 g/dL	– History of chronic liver disease – ESA treatment within 60 days – IV iron supplementation within 60 days – Red blood cell transfusion within 12 weeks – NYHA Class III or IV congestive heart failure – MI or acute coronary syndrome within 3 months – Thrombolytic events within 4 weeks – Uncontrolled hypertension – Any history of malignancy or genetic predisposition for developing cancer	**Hb Response:** Change from BL Hb of ≥1 g/dL at any time from day 1 of treatment through 2 weeks of follow-up
FGCL-4592-047 **NCT01599507** **Chen 2017**[42]	Phase IIb, double-blind, placebo controlled, parallel-arm trial Follow-Up: – Treatment period: 8 weeks – Post-treatment follow-up: NR	China	91	**Roxadustat, low dose (N=30)** – ≥40-<60 kg: 1.1-1.75 mg/kg TIW **Roxadustat, high dose (N=31)** – >60-≤80 kg: 1.50-2.25 mg/kg TIW – >80-≤100 kg: 1.50-2.25 mg/kg TIW **Placebo (n=30)**	– 18 – 80 years of age – CKD (stage 3 or 4) not on dialysis – eGFR ≥10 - <60 ml/min/1.73m^2 – Hb <10.0 g/dL	– ESA treatment within 12 weeks – IV iron supplementation within 4 weeks – RBC transfusion within 12 weeks or anticipated need – NYHA II or IV congestive heart failure – Thromboembolic event within 12 weeks – History of malignancy	**Hb Response:** Hb rise of _1.0 g/dL from baseline at any time
1517-CL-0303 **NCT01964196** **Akizawa 2019**[43]	Phase II, double-blind, placebo-controlled, parallel-arm trial Follow-Up:	Japan	107	Fixed-dose period **Roxadustat (N=80)** – 50 mg TIW – 70 mg TIW	– 20 – 74 years of age – CKD not on dialysis – eGFR ≤89 ml/min/1.73 m^2 – Hb <10.0 g/dL – TSAT ≥5%	– ESA treatment within 6 weeks – NYHA Class III or higher congestive heart failure – History of hospitalization for stroke, MI, or lung infarction within 24 weeks	**Hb response:** Hb ≥10.0 g/dL and increase in Hb from baseline ≥1 g/dL

Trial Name (NCT), Author	Study Design & Follow-Up Duration	Location	N	Arms	Key Inclusion Criteria	Key Exclusion Criteria	Definitions
	– Fixed-dose period: 6 weeks – Titration period: 18 weeks			– 100 mg TIW **Placebo (n=27)** <u>Titration period</u> **Roxadustat (N=55)** – 50 mg QW – 70 mg QW – 100 mg QW – 50 mg TIW – 70 mg TIW – 100 mg TIW **Placebo (N=1)**	– Ferritin ≥30 ng/mL	– Uncontrolled hypertension – History of malignancies	

BIW: twice weekly, CKD: chronic kidney disease, dL: deciliter, eGFR: estimated glomerular filtration rate, ESA: erythropoiesis-stimulating agent, g: gram, Hb: hemoglobin, IV: intravenous, kg: kilogram, m^2: square meter, mg: milligram, MI: myocardial infarction, min: minute, ml: milliliter, N: total number, NYHA: New York Heart Association, QW: weekly, TIW: thrice weekly, TSAT: transferrin saturation, ULN: upper limit of normal.

Evidence Table 2. Baseline Characteristics – Key Trials

Trial		ALPS[20,22,39]		ANDES[18,22]		DOLOMITES[21]		OLYMPUS[19,22,26]	
Arm		ROX (N=391)	PBO (N=203)	ROX (N=616)	PBO (N=306)	ROX (N=323)	DAR (N=293)	ROX (N=1384)	PBO (N=1377)
Age, mean years (SD)		60.6 (13.5)	61.7 (13.8)	64.9 (12.6)	64.8 (13.2)	66.8 (13.6)	65.7 (14.4)	60.9 (14.7)	62.4 (14.1)
Male, n (%)		169 (43.2)	99 (48.8)	241 (39.1)	130 (42.5)	145 (44.9)	129 (44.0)	564 (40.8)	603 (43.8)
White, n (%)		335 (85.7)	182 (89.7)	NR	NR	306 (94.7)	281 (95.9)	623 (45.0)	611 (44.4)
eGFR, mL/min/1.73 m², mean (SD)		16.5 (10.2)	17.2 (11.7)	21.9 (11.5)	22.4 (11.4)	20.3 (11.5)	20.3 (10.7)	19.7 (11.7)	20.0 (11.7)
Hb, mean g/dL (SD)		9.08 (0.8)	9.10 (0.7)	9.10 (0.75)	9.09 (0.69)	9.55 (0.80)	9.55 (0.7)	9.1 (0.7)	9.1 (0.7)
Hepcidin, mean ng/mL (SD)		37.85 (36.63)	41.16 (37.27)	NR		NR		163.16 (116.94)	155.45 (111.83)
TSAT, mean % (SD)		25.0 (95% CI: 24.0, 26.0)[§]	26.1 (95% CI: 24.2, 28.5)[§]	26.4 (10.9)	26.2 (11.3)	NR		NR	
Soluble Transferrin Receptor, ng/mL (SD)		4.05 (2.36)[#]	3.88 (1.95)[#]	NR		NR		NR	
Ferritin, mean ng/mL (SD)		241.72 (95% CI: 215.35, 266.99)[#§]	264.80 (NR)[#§]	308.6 (388.3)	308.4 (352.5)	NR		NR	
Iron Status - Replete*, n (%)		204 (52.2)	109 (53.7)	373 (60.6)	170 (55.6)	182 (56.3)	152 (51.9)	809 (58.5)	799 (58.0)
CRP	Mean mg/L (SD)	NR		NR		NR		7.0 (15.0)[‡]	7.0 (18.0)[‡]
	>ULN[†], n (%)	143 (36.9)	67 (33.2)	156 (25.3)	81 (26.5)	111 (34.7)	116 (39.6)	227 (16.4)	209 (15.2)
LDL-C, mean mg/dL (SD)		115.62 (49.88)	111.37 (44.08)	98.00 (39.1)	96.30 (40.00)	100.6 (40.0)	102.80 (39.80)	94.5 (NR)	92.5 (NR)
HDL-C, mean mg/dL (SD)		44.43 (13.42)[‡]	44.16 (12.84)[‡]	NR		NR		NR	
Total Cholesterol, mean mg/dL (SD)		NR		174.9 (48.4)	172.5 (52.5)	NR		NR	
No data reported for the following baseline characteristics: Transferrin, serum iron, total iron binding capacity									

DAR: darbepoetin alfa, CRP: C-reactive protein, dL: deciliter, eGFR: estimated glomerular filtration rate, g: gram, Hb: hemoglobin, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, mg: milligram, min: minute, mL: milliliter, n: number, N: total number, ng: nanogram, NR: not reported, NYHA: New York Heart Association, PBO: placebo, ROX: roxadustat, SD: standard deviation, TSAT: transferrin saturation

*Ferritin ≥100 ng/mL and TSAT ≥20%.

†Defined as 4.9 mg/L in ALPS, ANDES, and DOLOMITES; defined as 5.0 mg/L in OLYMPUS.

‡Converted to mg/L.

§Data are digitized and should be interpreted with caution.

#Converted to ng/mL.

Evidence Table 3. Baseline Characteristics – Other Phase III Trials

Trial		FGCL-4592-808[40]		1517-CL-0310[38]	
Arm		ROX (N=101)	PBO (N=51)	ROX (N=NR)	DAR (N=NR)
Age, mean years (SD)		54.7 (13.3)	53.2 (13.1)	NR	
Male, n (%)		36 (36.0)	20 (39.0)	NR	
White, n (%)		0 (0)†	0 (0)†	0 (0)†	0 (0)†
eGFR, ml/min/1.73 m^2, mean (SD)		16.5 (8.0)	14.5 (7.6)	NR	
Hb, mean g/dL (SD)		8.9 (0.8)	8.9 (0.7)	NR	
Hepcidin, mean ng/mL (SD)		95.9 (72.4)	114.7 (85.7)	NR	
TSAT, mean % (SD)		20.6 (9.2)	23.0 (11.1)	NR	
Ferritin, mean ng/mL (SD)		191.4 (200.5)	266.2 (236.7)	NR	
C-Reactive Protein	Mean mg/L (SD)	NR		NR	
	>ULN*, n (%)	12 (12.0)	5 (10.0)	NR	
Total Cholesterol, mean mg/dL (SD)		172.8 (45.80)	181.40 (49.0)	NR	
LDL-C, mean mg/dL (SD)		97.8 (34.0)	105.2 (42.2)	NR	
HDL-C, mean mg/dL (SD)		49.9 (14.6)	48.6 (16.3)	NR	
No data reported for the following baseline characteristics: transferrin, soluble transferrin receptor, serum iron, iron status – replete					

DAR: darbepoetin alfa, dL: deciliter, eGFR: estimated glomerular filtration rate, g: gram, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, m^2: square meter, mg: milligram, min: minute, mL: milliliter, n: number, N: total number, ng: nanogram, NR: not reported, PBO: placebo, ROX: roxadustat, SD: standard deviation

*Defined as of 4.9 mg/L.

†All patients were Asian.

Evidence Table 4. Baseline Characteristics – Phase II Trials

Trial	FGCL-SM4592-017[41]							FGCL-4592-047[42]			1517-CL-0303[43]			
Arm	ROX, 1.0 mg/kg BIW (N=12)	ROX, 1.0 mg/kg TIW (N=9)	ROX, 1.5 mg/kg BIW (N=10)	ROX, 1.5 mg/kg TIW (N=11)	ROX, 2.0 mg/kg BIW (N=11)	ROX, 2.0 mg/kg TIW (N=12)	PBO (N=28)	ROX, low-dose (N=30)	ROX, high-dose (N=31)	PBO (N=30)	ROX, 50 mg (N=27)	ROX, 70 mg (N=26)	ROX, 100 mg (N=27)	PBO (N=27)
Age, mean years (SD)	69.5 (Range: 52 - 80)	67.0 (Range: 54 - 79)	63.8 (Range: 52 - 77)	63.5 (Range: 49 - 72)	64.3 (Range: 53 - 82)	66.8 (Range: 49 - 76)	68.6 (Range: 56 - 79)	48.1 (13.0)	49.6 (14.8)	51.4 (11.9)	67.3 (7.7)	60.8 (8.8)	65.0 (8.5)	61.9 (10.6)
Male, n (%)	4 (33.3)	6 (66.7)	4 (40.0)	1 (9.1)	3 (27.3)	3 (25.0)	16 (57.1)	8 (26.7)	10 (32.3)	8 (26.7)	14 (51.9)	14 (53.8)	11 (40.7)	11 (40.7)
White, n (%)	6 (50.0)	5 (55.6)	7 (70.0)	4 (36.4)	8 (72.7)	6 (50.0)	15 (53.6)	0 (0)‡	0 (0)‡	0 (0)‡	0 (0)‡	0 (0)‡	0 (0)‡	0 (0)‡
eGFR, ml/min/1.73 m², mean (SD)	38.0 (15.5)	35.2 (9.7)	27.9 (8.2)	40.1 (15.3)	34.7 (15.1)	32.7 (9.9)	31.4 (12.4)	21.1 (10.2)	17.7 (8.6)	23.0 (13.4)	15.8 (6.3)	17.3 (9.5)	15.9 (7.5)	16.3 (8.5)
Hb, mean g/dL (SD)	10.4 (1.5)	10.6 (0.9)	10.3 (0.6)	10.1 (0.7)	10.3 (1.0)	10.1 (1.1)	10.3 (0.9)	8.8 (0.9)	8.8 (0.9)	8.9 (0.8)	9.4 (0.6)	9.4 (0.6)	9.4 (0.5)	9.3 (0.7)
Hepcidin, mean ng/mL (SD)	NR							69.0 (13.1)	73.9 (12.1)	69.9 (8.7)	37.8 (21.3)	45.9 (25.8)	36.3 (25.3)	40.9 (26.2)
Transferrin, mean mg/L (SD)	NR							2.33 (0.49)	2.19 (0.35)	2.16 (0.45)	NR			
TSAT, mean % (SD)	24.0 (9.4)	23.5 (5.2)	31.1 (8.1)	25.8 (6.5)	30.0 (9.3)	31.6 (11.0)	28.3 (6.8)	22.1 (11.4)	24.2 (8.8)	21.9 (6.3)	28.3 (8.2)	29.7 (10.0)	31.1 (11.8)	26.8 (10.6)
Soluble Transferrin Receptor, mean mg/L (SD)	NR							3.7 (1.9)	3.5 (1.4)	3.5 (1.2)	NR			
Serum Iron, mean µg/dL (SD)	69.1 (17.5)						71.1 (19.7)	61.0 (24.3)	64.9 (20.7)	58.1 (14.8)	NR			
Total Iron Binding Capacity, mean µg/dL (SD)	246.3 (43.5)						248.5 (51.6)	263.0 (52.0)	242.0 (37.0)	240.0 (49.0)	265.92 (54.75)#	254.19 (43.58)#	265.92 (50.28)#	253.63 (26.82)#

Trial		FGCL-SM4592-017[41]							FGCL-4592-047[42]			1517-CL-0303[43]			
Ferritin, mean ng/mL (SD)		174.0 (181.0)	167.0 (178.0)	228.0 (184.0)	184.0 (101.0)	242.0 (218.0)	190.0 (89.4)	228.0 (193.0)	201.0 (252.0)	184.0 (194.0)	221.0 (181.0)	119.7 (61.0)	144.4 (99.7)	129.8 (89.3)	125.4 (74.1)
CRP	**Mean mg/L (SD)**	NR							4.0 (12.8)	1.9 (3.8)	1.5 (2.2)	NR			
	>ULN[†], n (%)								NR						
Total Cholesterol, mean mg/dL (SD)		NR							164.0 (33.0)	169.0 (45.0)	183.0 (52.0)	NR			
LDL-C, mean mg/dL (SD)		NR							96.0 (24.0)	110.0 (36.0)	115.0 (40.0)	NR			
HDL-C, mean mg/dL (SD)		NR							54.0 (20.0)	44.0 (17.0)	48.0 (19.0)	NR			
No data reported on the following baseline characteristics: number of patients who are iron replete, non-HDL-cholesterol															

CRP: C-reactive protein, DAR: darbepoetin alfa, dL: deciliter, eGFR: estimated glomerular filtration rate, g: gram, HDL-C: high-density lipoprotein cholesterol, L: liter, LDL-C: low-density lipoprotein cholesterol, µg: microgram, mg: milligram, min: minute, mL: milliliter, n: number, N: total number, ng: nanogram, NR: not reported, PBO: placebo, ROX: roxadustat, SD: standard deviation

*****Data for ROX, 0.7 mg/kg BIW and ROX, 0.7 mg/kg TIW not abstracted.

†Defined as 4.9 mg/L.

‡All patients were Asian.

#Converted from µmol/L to µg/dL.

Evidence Table 5. Efficacy Outcomes – Key Trials

Trial			ALPS[20,22,23,39]		ANDES[18,22]		DOLOMITES[21]		OLYMPUS[19,22,26,49]	
Arm			ROX	PBO	ROX	PBO	ROX	DAR	ROX	PBO
Change in Hb, g/dL	Timepoint		Average of 28 to 52 Weeks		Average of 28 to 52 Weeks		Average of 28 to 36 Weeks		Average of 28 to 52 Weeks	
	N		312	146	608	305	323	293	1334	1330
	LSM (SE)		Mean (SD): 2.00 (0.95)	Mean (SD): 0.41 (0.98)	2.02 (0.04)	0.17 (0.05)	1.85 (NR)	1.84 (NR)	1.75 (SD: 0.03)	0.40 (SD: 0.03)
	Between Group Diff.	LSM (95% CI), p-value	1.69 (1.52, 1.86), <0.001		1.85 (1.74, 1.97), <0.0001		0.02 (-0.13, 0.16), NR		1.35 (1.27, 1.43), <0.001	
Hb Response	Timepoint		24 Weeks							
	N		389	203	608	305	286	273	1371	1357
	n (%)		308 (79.2)	20 (9.9)	523 (86.0)	20 (6.6)	256 (89.5)	213 (78)	1055 (77.0)	112 (8.5)
	Between Group Diff.	% (95% CI), p-value	69.3 (63.6, 75.1), <0.001		79.5 (75.6, 83.4), <0.0001		11.51 (5.66, 17.36), <0.05		68.5 (NR), <0.001	
Change in eGFR, mL/min/1.73 m^2	Timepoint		108 Weeks		NR		NR		Treatment period	
	N		389	203					1326	1314
	LSM (95% CI)		-2.65 (3.29, -2.02)	-3.24 (-4.21, -2.28)					Mean (SD): -3.70 (NR)	Mean (SD): -3.19 (NR)
	Between Group Diff.	LSM (95% CI), p-value	0.59 (-0.57, 1.75), 0.316						Mean: -0.51 (-1.00, -0.01), 0.046	
CKD Progression	Timepoint		2 Years		NR		NR		NR	
	N		389	203						
	% (95% CI)		58.9 (52.7, 65.1)	61.1 (50.5, 71.7)						
	Between Group Diff.	HR (95% CI), p-value	1.00 (0.76, 1.30), 0.972							
Use of Rescue Therapy	Timepoint		52 Weeks				NR		On treatment* + 28 days	
	N		323	203	608	305			1384	1376

Trial			ALPS[20,22,23,39]		ANDES[18,22]		DOLOMITES[21]		OLYMPUS[19,22,26,49]	
Arm			ROX	PBO	ROX	PBO	ROX	DAR	ROX	PBO
	n (%)		53 (16.5)	93 (45.8)	54 (8.9)	88 (28.9)			254 (18.4)	574 (41.7)
	Between Group Diff.	HR (95% CI), p-value	0.24 (0.17, 0.33), <0.001		0.19 (0.14, 0.28), <0.0001				0.26 (0.23, 0.31), <0.001	
Use of Blood Transfusion	Timepoint		52 Weeks				NR		On treatment* + 28 days	
	N		389	203	616	305			1384	1376
	n (%)		160 (41.2)	126 (62.1)	55 (5.6)	88 (15.4)			176 (12.7)	320 (23.3)
	Time to Event	HR (95% CI), p-value	0.34 (0.21, 0.55), <0.001		0.26 (0.17, 0.41), <0.0001				0.37 (0.30, 0.44), <0.001	
Use of IV Iron	Timepoint		104 Weeks		52 Weeks		36 weeks		On treatment* + 28 days	
	N		389	203	608	305	323	293	1384	1376
	n (%)		41 (10.6)	39 (19.1)	15 (2.5)	15 (4.9)	32 (9.9)	62 (21.2)	59 (4.3)	108 (7.9)
	Time to Event	HR (95% CI), p-value	0.54 (0.29, 0.99), 0.045		0.39 (0.19, 0.81), 0.011		0.45 (0.26, 0.78), 0.004		0.41 (0.29, 0.56), <0.001	
Use of ESA Treatment	Timepoint		104 Weeks		52 Weeks		NR		On treatment* + 28 days	
	N		389	203	616	305			1384	1376
	n (%)		26 (6.7)	86 (42.3)	13 (2.1)	20 (6.7)			65 (4.7)	324 (23.6)
	Time to Event	HR (95% CI), p-value	0.10 (0.06, 0.17), <0.001		0.08 (0.04, 0.15), <0.001				0.13 (0.10, 0.18), <0.001	
Change in Hepcidin	Timepoint		104 Weeks		44 Weeks		NR		24 weeks	
	N		108	28	396	152			658	604
	Mean ng/mL (SD)		-10.05 (33.67)	-7.44 (22.92)	LSM: -18.83 (SEM: 4.37)	LSM: 6.89 (SEM: 6.21)			LSM (SD): -35.94 (116.69)	LSM (SD): 9.42 (115.78)
	Between Group Diff.	LSM (95% CI), p-value	NR		-25.71 (-38.52, -12.90), <0.0001				-45.36 (-56.24, -34.49), <0.001	
Change in Transferrin Saturation	Timepoint		104 Weeks		44 Weeks		NR		Average of 24 Weeks to EOT¤	
	N		112	29	476	185			1199	1047
	Mean % (SD)		-0.4 (12.6)	0.0 (12.3)	LSM: 0.41 (SEM 0.64)	LSM: 0.53 (SEM: 0.90)			-0.83 (NR)	-0.26 (NR)

Trial			ALPS[20,22,23,39]		ANDES[18,22]		DOLOMITES[21]		OLYMPUS[19,22,26,49]	
Arm			ROX	PBO	ROX	PBO	ROX	DAR	ROX	PBO
	Between Group Diff.	LSM (95% CI), p-value	NR		-0.12 (-1.96, 1.72), 0.8984				-0.57 (-1.31, 0.18), 0.134	
Change in Soluble Transferrin Receptor, ng/mL	Timepoint		104 weeks		NR		NR		NR	
	N		391	203						
	Mean (95% CI)		2.37 (NR)[#§]	0.33 (NR)[#§]						
	Between Group Diff.	LSM (95% CI), p-value	NR							
Change in Serum Iron, µg/dL	Timepoint		44 Weeks						Average of 24 Weeks to EOT[¤]	
	N		NR		480	188	NR		1201	1050
	LSM (SEM)				10.38 (1.91)	2.12 (2.66)			6.63 (NR)	-1.07 (NR)
	Between Group Diff.	LSM (95% CI), p-value			8.26, (2.89, 13.63), 0.0026				7.70 (5.82, 9.58), <0.001	
Change in Total Iron Binding Capacity, µg/dL	Timepoint		44 Weeks						Average of 24 Weeks to EOT[¤]	
	N		NR		476	185	NR		1200	1050
	LSM (SEM)				35.07 (2.52)	-3.58 (3.44)			30.79 (NR)	-3.82 (NR)
	Between Group Diff.	LSM (95% CI), p-value			38.65 (31.86, 45.45), <0.0001				34.61 (31.29, 37.93)	
Change in Ferritin, ng/mL	Timepoint		104 Weeks		44 Weeks		NR		Average of 24 Weeks to EOT[¤]	
	N		112	30	478	187	NR		1200	1050
	Mean (95% CI)		-115.70 (NR)[†**]	-61.86 (NR)[†]	LSM: -44.60 (SEM: 12.36)	LSM: 12.94 (SEM: 16.97)			-37.10 (NR)	17.45 (NR)
	Between Group Diff.	LSM (95% CI), p-value	NR		-57.54 (-92.80, -22.29), 0.0014				-54.55 (-71.68, -37.42), <0.001	
Change in Total Cholesterol, mg/dL	Timepoint		104 Weeks		52 Weeks		NR			
	N		123	32	616	306	NR		NR	
	Mean (SD)		-36.50 (61.25)[#]	8.43 (1.07)[#]	-27.20 (45.79)	-3.21 (49.78)				

Trial			ALPS[20,22,23,39]		ANDES[18,22]		DOLOMITES[21]		OLYMPUS[19,22,26,49]	
Arm			ROX	PBO	ROX	PBO	ROX	DAR	ROX	PBO
	Between Group Diff.	LSM (95% CI), p-value	NR		NR					
Change in LDL-C, mg/dL	Timepoint		Average of 12 - 28 weeks						24 weeks	
	N		391	203	564	269	323	293	1147	1133
	Mean (SD)		-23.28# (NR)	5.84# (NR)	-18.48 (29.60)	0.22 (29.37)	LSM: -13.77# (NR)	LSM: 1.82# (NR)	LSM: -14.58 (SE: 1.08)	LSM: -0.70 (SE: 1.04)
	Between Group Diff.	LSM (95% CI), p-value	-27.11 (-32.10, -22.04), <0.001		-17.26 (-20.65, -13.87) <0.0001		-15.584 (-19.72, -11.45), <0.001		-13.88 (-16.37, -11.39), <0.001	
Change in HDL-C, mg/dL	Timepoint		104 weeks		NR					
	N		123	32						
	Mean (SD)		-4.02 (10.17)#	1.66 (10.05)#						
	Between Group Diff.	LSM (95% CI), p-value	NR							
Data not reported for the following outcomes: Change in transferrin										

100PY: 100 person-years, 95% CI: 95% confidence interval, DAR: darbepoetin alfa, diff.: difference, dL: deciliter, eGFR: estimated glomerular filtration rate, Ep100PY: events per 100 person years, g: gram, Hb: hemoglobin, HDL-C: high-density lipoprotein cholesterol, HR: hazard ratio, IR: incidence rate, IV: intravenous, LDL-C: low-density lipoprotein cholesterol, LS: least squares, µg: microgram, mg: milligram, min: minute, mL: milliliter, n: number, N: total number, ng: nanogram, NR: not reported, ns: not significant, PBO: placebo, ROX: roxadustat, SD: standard deviation

*Up to 4.5 years.

†Converted to ng/mL.

‡Up to 3 years.

§Doubling serum creatinine, chronic dialysis or renal transplant, and death.

#Converted to mg/dL.

¤Up to 4.5 years.

**Data are digitized and should be interpreted with caution.

Evidence Table 6. Change in Hb – Subgroups I

Trial			ALPS[20]						OLYMPUS[19,22]					
Subgroups			Iron Replete*		Iron Deplete†		CRP >ULN‡		Iron Deplete†		Iron Replete§		CRP >ULN‡	
Arm			ROX (N=204)	PBO (N=109)	ROX (NR)	PBO (NR)	ROX (N=143)	PBO (N=67)	ROX (N= 552)	PBO (N= 560)	ROX (N=809)	PBO (N=799)	ROX (N=227)	PBO (N=209)
Timepoint			Average of Weeks 28 to 52						Average of Weeks 28 to 36				Average of Weeks 28 to 52	
Change in Hb, g/dL	LSM (95% CI)		1.97 (1.74, 2.20)	0.25 (-0.04, 0.54)	1.99 (1.69, 2.29)	0.35 (-0.03, 0.73)	1.92 (1.48, 2.35)	0.02 (-0.65, 0.69)	Mean: 1.76 (NR)	Mean: 0.43 (NR)	Mean: 1.71 (NR)	Mean: 0.39 (NR)	LSM: 1.73 (SE: 0.09)	LSM: 0.62 (SE: 0.09)
	Btw. Group Diff.	LSM (95% CI), p-value	1.72 (1.47, 1.97), NR		1.64 (1.35, 1.92), NR		1.90 (1.42, 2.38)		1.33 (1.21, 1.45), <0.001		1.33 (1.22, 1.45), <0.001		1.10 (0.90, 1.30), <0.001	

95% CI: 95% confidence interval, btw.: between, diff.: difference, dL: deciliter, g: gram, Hb: hemoglobin, LSM: least squares mean, N: total number, NR: not reported, ns: not significant, PBO: placebo, ROX: roxadustat, SD: standard deviation

*Ferritin ≥100 ng/mL and TSAT ≥20%.

†Ferritin <100 ng/mL or TSAT <20%.

‡Defined as 5.0 mg/L.

§Ferritin ≥100 ng/mL or TSAT ≥20%.

Evidence Table 7. Change in Hb – Subgroups II

Trial			ANDES[18]													
Subgroups			Iron Deplete†		Iron Replete*		CRP ≤ULN‡		CRP >ULN‡		CKD Stage 3		CKD Stage 4		CKD Stage 5	
Arm			ROX (N=NR)	PBO (N=NR)	ROX (N=NR)	PBO (N=NR)	ROX (N=NR)	PBO (N=NR)	ROX (N=NR)	PBO (N=NR)	ROX (N=NR)	PBO (N=NR)	ROX (N=NR)	PBO (N=NR)	ROX (N=NR)	PBO (N=NR)
Timepoint			Average of Weeks 28 to 52													
Change in Hb, g/dL	Mean (SD)		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Btw. Group Diff.	Treatment Difference Estimate (95% CI), p-value	1.64 (1.46, 1.83), NR		2.02 (1.88, 2.17), NR		1.84 (1.71, 1.97), NR		1.90 (1.66, 2.14), NR		1.53 (1.29, 1.77), NR		1.81 (1.65, 1.98), NR		2.16 (1.94, 2.39), NR	

95% CI: 95% confidence interval, CRP: C-reactive protein btw.: between, diff.: difference, dL: deciliter, g: gram, Hb: hemoglobin, N: total number, NR: not reported, ns: not significant, PBO: placebo, ROX: roxadustat, SD: standard deviation

*Ferritin ≥100 ng/mL or TSAT ≥20%.

†Ferritin <100 ng/mL or TSAT <20%.

‡Defined as 4.9 mg/L.

Evidence Table 8. Efficacy Outcomes – Other Phase III Trials

Trial			FGCL-4592-808[40]		1517-CL-0310[38]	
Arm			ROX	PBO	ROX	DAR
Change in Hb, g/dL	Timepoint		Average of Weeks 7 to 9		Average of Weeks 18 to 24	
	N		93	46	NR	NR
	LSM (SE)		1.80 (0.1)	-0.50 (0.20)	NR	NR
	Between Group Difference	LSM (95% CI), p-value	2.30 (1.9, 2.6), <0.0001		Mean: -0.07 (-0.23, 0.10), NR	
Hb Response	Timepoint		9 Weeks		NR	
	N		101	50		
	n (%)		85 (84)	0 (0)		
	Between Group Difference	Mean % (95% CI), p-value	84 (75.00, 91.00), NR			
Use of Rescue Therapy	Timepoint		27 Weeks		NR	
	N		NR	NR		
	n (%)		3 (3.0)	6 (12.0)		
	Between Group Difference	HR (95% CI), p-value	0.11 (0.02, 0.51), NR			
Change in Hepcidin, ng/mL	Timepoint		9 Weeks		NR	
	N		86	44		
	Mean (SD)		-56.14 (63.40)	-15.10 (48.06)		
	Between Group Difference	LSM (95% CI), p-value	-49.77 (-66.75, -32.79), NR			
Change in Transferrin, mg/L	Timepoint		9 Weeks		NR	
	N		85	43		
	Mean (SD)		0.73 (0.48)	-0.01 (0.39)		
	Between Group Difference	LSM (95% CI), p-value	0.75 (0.59, 0.92), NR			
Change in Transferrin Saturation, %	Timepoint		9 Weeks		NR	
	N		85	43		
	Mean (SD)		-5.2 (10.4)	-1.7 (9.2)		

Trial			FGCL-4592-808[40]		1517-CL-0310[38]	
Arm			ROX	PBO	ROX	DAR
	Between Group Difference	LSM (95% CI), p-value	-4.3 (-7.4, -1.1), NR			
Change in Serum Iron, µg/dL	Timepoint		9 Weeks		NR	
	N		85	43		
	Mean (SD)		-1.34 (35.25)*	-3.58 (24.36)*		
	Between Group Difference	LSM (95% CI), p-value	1.34 (-9.33, 12.01)*, NR			
Change in Total Iron Binding Capacity, µg/dL	Timepoint		9 Weeks		NR	
	N		85	43		
	Mean (SD)		101.68 (66.82)*	-1.84 (54.3)*		
	Between Group Difference	LSM (95% CI), p-value	105.53 (82.63, 128.38)*, NR			
Change in Ferritin, ng/mL	Timepoint		9 Weeks		NR	
	N		85	43		
	Mean (SD)		-93.3 (146.3)	-21.9 (115.5)		
	Between Group Difference	LSM (95% CI), p-value	-102.2 (-142.6, -61.7), NR			
Change in Total Cholesterol, mg/dL	Timepoint		9 Weeks		NR	
	N		101	50		
	Mean (SD)		-40.6 (NR)	-7.7 (NR)		
	Between Group Difference	Mean (95% CI), p-value	-32.9 (-1.1, -0.6), NR			
Change in LDL-C, mg/dL	Timepoint		9 Weeks		NR	
	N		101	50		
	Mean (SD)		-25.3 (NR)	-5.8 (NR)		
	Between Group Difference	Mean (95% CI), p-value	-21.2 (-0.8, -0.3), NR			
Data not reported for the following outcomes: Change in eGFR, use of RBC transfusion, use of ESA treatment, use of IV iron, change in soluble transferrin receptor, change in HDL-cholesterol						

95% CI: 95% confidence interval, DAR: darbepoetin alfa, dL: deciliter, eGFR: estimated glomerular filtration rate, Ep100PY: events per 100 person years, g: gram, Hb: hemoglobin, HDL-C: high-density lipoprotein cholesterol, HR: hazard ratio, IV: intravenous, LDL-C: low-density lipoprotein cholesterol, LS: least squares, µg: microgram, mg: milligram, min: minute, mL: milliliter, n: number, N: total number, ng: nanogram, NR: not reported, ns: not significant, PBO: placebo, ROX: roxadustat, SD: standard deviation

*Converted from µmol/L to µg/mL.

Evidence Table 9. Efficacy Outcomes – Phase II Trials

Trial			FGCL-SM4592-017‡[41]							FGCL-4592-047[42]			1517-CL-0303[43]			
Arm			ROX, 1.0 mg/kg BIW	ROX, 1.0 mg/kg TIW	ROX, 1.5 mg/kg BIW	ROX, 1.5 mg/kg TIW	ROX, 2.0 mg/kg BIW	ROX, 2.0 mg/kg TIW	PBO	ROX, Low-Dose	ROX, High-Dose	PBO	ROX, 50 mg	ROX, 70 mg	ROX, 100 mg	PBO
Change in Hb, g/dL	Timepoint		6 Weeks							8 Weeks			Average of 18-24 Weeks			
	N		12	9	10	11	11	12	28	30	31	30	27	26	27	27
	Mean (SD)		NR	0.41 (SE: 0.59) *, ns	NR	1.20 (SE: 0.22)*, <0.01	NR	1.80 (SE: 0.30) *, <0.01	-0.10 (SE: 0.13)*	1.55 (1.23)	2.38 (1.46)	0.37 (0.87)	1.10 (0.71)	1.33 (0.82)	1.55 (0.88)	-0.17 (0.61)
	Between Group Diff.	LSM (95% CI), p-value	NR						---	NR, <0.0001	NR, <0.0001	--	NR, <0.001	NR, <0.001	NR, <0.001	--
Hb Response	Timepoint		6 Weeks							8 Weeks			24 Weeks			
	N		5	5	10	11	9	11	23	30	31	30	27	26	27	27
	n (%)		3 (60.0)	2 (40.0)	8 (80.0)	10 (91.0)	9 (100)	11 (100)	3 (13.0)	24 (80.0)	27 (87.1)	7 (23.3)	22 (81.5)	26 (100)	27 (100)	4 (14.8)
	Between Group Diff.	Mean % (95% CI), p-value	NR, 0.018	NR, ns	NR, <0.001	NR, <0.001	NR, <0.001	NR, <0.001	--	NR, 0.0004	NR, <0.0001	--	NR, <0.001	NR, <0.001	NR, <0.001	--
Use of Rescue Therapy	Timepoint		12 Weeks							8 weeks			NR			
	N		Rescue therapy not permitted during 4-week treatment period and 4 weeks post-treatment							NR	NR	NR				
	n (%)									1 (3.3)	0 (0)	1 (3.3)				
	Time to Event	HR (95% CI) p-value								NR	NR	---				
Use of ESA Treatment	Timepoint		8 to 12 Weeks							NR			NR			
	N		NR						NR							
	n (%)		8 (9.1)						5 (17.9)							

Trial			FGCL-SM4592-017‡[41]							FGCL-4592-047[42]			1517-CL-0303[43]			
Arm			ROX, 1.0 mg/kg BIW	ROX, 1.0 mg/kg TIW	ROX, 1.5 mg/kg BIW	ROX, 1.5 mg/kg TIW	ROX, 2.0 mg/kg BIW	ROX, 2.0 mg/kg TIW	PBO	ROX, Low-Dose	ROX, High-Dose	PBO	ROX, 50 mg	ROX, 70 mg	ROX, 100 mg	PBO
	Time to Event	HR (95% CI), p-value	NR													
Change in Hepcidin, ng/mL	Timepoint		4 weeks							8 weeks			24 weeks			
	N		NR		NR		NR		23	30	31	30	27	26	27	27
	Mean (SD)		NR		-150 (89.5)		-225 (192)		-17.8 (114)	-37.8 (9.9)	-37.2 (9.3)	-4.8 (8.2)	-12.5 (24.3)	-3.3 (31.9)	-13 (23.3)	2.4 (39.6)
	Between Group Diff.	LSM (95% CI), p-value	NR		NR, p=0.048		NR, 0.0013		--	NR, 0.0004	NR, 0.0003	--	NR, ns	NR, ns	NR, ns	---
Change in Transferrin, mg/L	Timepoint		NR							8 weeks			24 weeks			
	N									30	31	30	27	26	27	27
	Mean (SD)									0.67 (0.49)	0.96 (0.54)	0.02 (0.22)	0.4 (0.4)	0.2 (0.4)	0.3 (0.3)	0.03 (0.2)
	Between Group Diff.	LSM (95% CI), p-value								NR, <0.0001	NR, <0.0001	--	NR, <0.001	NR, ns	NR, <0.001	---
Change in Transferrin Saturation, %	Timepoint		4 weeks							8 weeks			24 weeks			
	N		67						18	30	31	61	27	26	27	27
	Mean (SD)		−8.1 (9.3)						-3.1 (7.8)	-3.9 (9.7)	-8.7 (9.5)	0.2 (7.9)	-4.2 (6.8)	1 (14.9)	-0.2 (13.3)	0.2 (10.2)
	Between Group Diff.	LSM (95% CI), p-value	NR, p=0.036						--	NR, 0.11	NR, <0.0001	-- --	NR, 0.004	NR, 0.73	NR, 0.93	---
Change in Soluble	Timepoint		NR							8 weeks			NR			
	N									30	31	61				

Trial			FGCL-SM4592-017‡[41]							FGCL-4592-047[42]			1517-CL-0303[43]			
Arm			ROX, 1.0 mg/kg BIW	ROX, 1.0 mg/kg TIW	ROX, 1.5 mg/kg BIW	ROX, 1.5 mg/kg TIW	ROX, 2.0 mg/kg BIW	ROX, 2.0 mg/kg TIW	PBO	ROX, Low-Dose	ROX, High-Dose	PBO	ROX, 50 mg	ROX, 70 mg	ROX, 100 mg	PBO
Transferrin Receptor, mg/L	Mean (SD)									2.7 (2.2)	3.7 (3.0)	0.05 (0.6)				
	Between Group Diff.	LSM (95% CI), p-value								NR, <0.0001	NR, <0.0001	--				
Change in Serum Iron, µg/dL	Timepoint		4 weeks							8 weeks			NR			
	N		67						18	30	31	30				
	Mean (SD)		64.1 (19.4)						-9.5 (19.3)	0.2 (23.9)	-8.1 (28.7)	2.7 (23.7)				
	Between Group Diff.	LSM (95% CI), p-value	NR						--	NR						
Change in Total Iron Binding Capacity, µg/dL	Timepoint		4 weeks							8 weeks			24 weeks			
	N		67						18	30	31	30	27	26	27	27
	Mean (SD)		41.8 (45.4)						-7.6 (26.6)	65.1 (47.9)	102 (56.2)	1.2 (22.1)	51.4 (46.93)†	25.7 (49.72)†	34.08 (36.31)†	5.03 (21.79)†
	Between Group Diff.	LSM (95% CI), p-value	NR, <0.0001						--	NR, <0.0001	NR, <0.0001	--	NR, <0.001	NR, 0.01	NR, <0.001	---
Change in Ferritin, ng/mL	Timepoint		4 weeks							8 weeks			24 weeks			
	N		67						18	30	31	30	27	26	27	27
	Mean (SD)		−68.8 (70.1)						-37.8 (40.3)	-124.0 (171.0)	-98.0 (81.0)	-28.0 (64.0)	-38.5 (44.9)	-23.4 (52.7)	-35.9 (63.4)	-16.5 (32.5)
	Between Group Diff.	LSM (95% CI), p-value	NR						--	NR, <0.0001	NR, <0.0001	--	NR, <0.05	NR, <0.001	NR, 0.03	--

Trial			FGCL-SM4592-017‡[41]							FGCL-4592-047[42]			1517-CL-0303[43]			
Arm			ROX, 1.0 mg/kg BIW	ROX, 1.0 mg/kg TIW	ROX, 1.5 mg/kg BIW	ROX, 1.5 mg/kg TIW	ROX, 2.0 mg/kg BIW	ROX, 2.0 mg/kg TIW	PBO	ROX, Low-Dose	ROX, High-Dose	PBO	ROX, 50 mg	ROX, 70 mg	ROX, 100 mg	PBO
Change in Total Cholesterol, mg/dL	Timepoint		NR							8 weeks			NR			
	N									30	31	61				
	Mean (SD)									-31.7 (25.3)	-35.6 (37.5)	8.0 (30)				
	Between Group Diff.	LSM (95% CI), p-value								NR, <0.0001	NR, <0.0001	--				
Change in LDL-C, mg/dL	Timepoint		NR							8 weeks			NR			
	N									30	31	30				
	Mean (SD)									-22.4 (19.4)#	-32 (33.5)#	4.0 (25.5)#				
	Between Group Diff.	LSM (95% CI), p-value								NR, <0.0001	NR, <0.0001	--				
Change in HDL-C, mg/dL	Timepoint		NR							8 weeks			NR			
	N									30	31	30				
	Mean (SD)									-7.7 (10.5)	-6.9 (7.0)	1.7 (10.6)				
	Between Group Diff.	LSM (95% CI), p-value								NR, 0.0001	NR, 0.0002	--				
Data on the following outcomes not reported: change in eGFR, use of blood transfusion, use of IV iron																

95% CI: 95% confidence interval, DAR: darbepoetin alfa, diff.: difference, dL: deciliter, eGFR: estimated glomerular filtration rate, Ep100PY: events per 100 person years, g: gram, Hb: hemoglobin, HDL-C: high-density lipoprotein cholesterol, HR: hazard ratio, IV: intravenous, LDL-C: low-density lipoprotein cholesterol, LS: least squares, µg: microgram, mg: milligram, min: minute, mL: milliliter, n: number, N: total number, ng: nanogram, NR: not reported, ns: not significant, PBO: placebo, ROX: roxadustat, SD: standard deviation

*Data are digitized and should be interpreted with caution.

†Converted from µmol/L to µg/dL.

‡Data for ROX, 0.7 mg/kg BIW and ROX, 0.7 mg/kg TIW not abstracted.

#Converted from mmol/L to mg/dL.

Evidence Table 10. Patient Reported Outcomes – Key Trials

Trial			ALPS[20,22,39]		ANDES[18]		DOLOMITES[21]		OLYMPUS[19,22,49]	
Arm			ROX (N=340)	PBO (N=185)	ROX (N=608)	PBO (N=306)	ROX (N=323)	DAR (N=293)	ROX (N=1279)	PBO (N=1235)
Timepoint			Average of 12-28 weeks							
Change in SF-36 Physical Functioning, Points	LSM (SE)		1.34 (95% CI: 0.15, 2.54)	0.63 (95% CI: -0.76, 2.03)	NR		1.03 (NR)	2.31 (NR)	0.14 (0.22)	-0.39 (0.23)
	Between Group Diff.	LSM (95% CI), p-value	0.71 (-0.56, 1.98), 0.27				-1.28 (-2.42, -0.15), NR		0.52 (0.00, 1.05), 0.051	
Change in SF-36 Physical Component Score, Points	LSM (95% CI)		1.84 (0.88, 2.80)	1.47 (0.34, 2.59)	NR		NR		NR	
	Between Group Diff.	LSM 95% CI), p-value	0.37 (-0.65, 1.40), 0.475							
Change in SF-36 Vitality, Points	LSM (SE)		2.79 (95% CI: 1.56, 4.01)	1.67 (95% CI: 0.23, 3.10)	Mean (SD): 1.90 (8.71)	Mean (SD): 1.02 (8.33)	3.89 (NR)	4.35 (NR)	1.59 (0.23)	1.15 (0.23)
	Between Group Diff.	LSM (95% CI), p-value	1.13 (-0.19, 2.44), 0.093		1.22 (0.15, 2.29), 0.0259		-0.457 (-1.66, 0.74), NR		0.44 (-0.11, 0.99), 0.12	
Change in FACT-An Anemia, Points	LSM (95% CI)		4.47 (2.86, 6.08); [N=339]	2.77 (0.91, 4.62)	NR		NR		NR	
	Between Group Diff.	LSM 95% CI), p-value	1.70 (0.02, 3.38), 0.047							

Trial			ALPS[20,22,39]		ANDES[18]		DOLOMITES[21]		OLYMPUS[19,22,49]	
Arm			ROX (N=340)	PBO (N=185)	ROX (N=608)	PBO (N=306)	ROX (N=323)	DAR (N=293)	ROX (N=1279)	PBO (N=1235)
Timepoint			Average of 12-28 weeks							
Change in FACT-An Total Score, Points	LSM (95% CI)		5.78 (2.60, 8.95); [N=338]	3.70 (0.01, 7.37)	NR		NR		NR	
	Between Group Diff.	LSM 95% CI), p-value	2.09 (-1.29, 5.46), 0.225							
Change in EQ-5D 5L, VAS	Mean (SD)		5.40 (17.28)	0.99 (15.86); [N=184]	NR		NR		NR	
	Between Group Diff.	LSM 95% CI), p-value	NR							
Improvement in PGIC, %	n (%)		180/389 (46.4)*	38/203 (28.6)*	NR		NR		NR	
	Between Group Diff.	LSM 95% CI), p-value	NR							
Other subscales not reported										

95% CI: 95% confidence interval, DAR: darbepoetin alfa, diff.: difference, LS: least squares, µg: microgram, N: total number, n: number, NR: not reported, PBO: placebo, ROX: roxadustat, SD: standard deviation

*At 28 weeks.

Evidence Table 11. CV Safety – Key Trials

Trial			ALPS[23]		ANDES[18,22]		DOLOMITES[21]		OLYMPUS[19,22,49]	
Arm			ROX (N=391)	PBO (N=203)	ROX (N=611)	PBO (N=305)	ROX (N=323)	DAR (N=293)	ROX (N=1384)	PBO (N=1377)
MACE*	n (%)		NR		NR		38 (11.8)	41 (14.0)	NR	
	Time to Event	HR (95% CI), p-value					0.81 (0.52, 1.25), 0.339			
MACE+[†]	n (%)		NR		NR		54 (16.7)	53 (18.1)	NR	
	Time to Event	HR (95% CI), p-value					0.9 (0.61, 1.32), 0.583			
MI	n (%)		14 (3.5)[‡]	5 (2.5)[‡]	5 (0.8)[§]	3 (1.0)[§]	11 (3.4)	10 (3.4)	40 (2.9)[‡]	40 (2.9)[‡]
	Time to Event	HR (95% CI), p-value	NR				0.96 (0.41, 2.27), 0.931		NR	
Stroke	n (%)		6 (1.5)[¶]	2 (0.9)[¶]	NR		4 (1.2)	7 (2.4)	15 (1.1)[#]	13 (0.9)[#]
	Time to Event	HR (95% CI), p-value	NR				0.48 (0.14, 1.67), 0.25		NR	
Heart Failure	n (%)		8 (2.1)§§	5 (2.46)§§	23 (3.8)[¶¶]	5 (1.6)[¶¶]	NR		70 (5.1)[§§]	82 (6.0)[§§]
	Time to Event	HR (95% CI), p-value	NR						NR	
Unstable Angina	n (%)		0 (0)	1 (0.5)	NR		NR		10 (0.7)	10 (0.7)
	Time to Event	HR (95% CI), p-value	NR						NR	
Heart Failure Requiring Hospitalization	n (%)		NR		NR		25 (7.7)	21 (7.2)	NR	
	Time to Event	HR (95% CI), p-value					1.08 (0.60, 1.95), 0.789			
	n (%)		NR		NR		0 (0)	1 (0.3)	NR	

Trial			ALPS[23]		ANDES[18,22]		DOLOMITES[21]		OLYMPUS[19,22,49]	
Arm			ROX (N=391)	PBO (N=203)	ROX (N=611)	PBO (N=305)	ROX (N=323)	DAR (N=293)	ROX (N=1384)	PBO (N=1377)
Unstable Angina Requiring Hospitalization	**Time to Event**	**HR (95% CI), p-value**					NR			
Data for cardiovascular mortality not reported										

95% CI: 95% confidence interval, DAR: darbepoetin alfa, HR: hazard ratio, MI: myocardial infarction, MACE: major adverse cardiovascular event, n: number, N: total number, NR: not reported, PBO: placebo, ROX: roxadustat

*Defined as all-cause mortality (not cardiovascular mortality), MI, or stroke.

†Defined as MACE or unstable angina requiring hospitalization or congestive heart failure requiring hospitalization.

‡Includes acute myocardial infarction and MI.

§Acute MI.

¶Includes hemorrhagic stroke and ischemic stroke.

#Includes cerebellar stroke, hemorrhagic stroke, ischemic stroke, and lacunar stroke.

§§Includes cardiac failure, cardiac failure acute, cardiac failure chronic, and cardiac failure congestive.

¶¶Cardiac failure congestive.

Evidence Table 12. CV Safety – Other Phase III Trials

Trial			FGCL-4592-808[40]		1517-CL-0310[38]	
Arm			ROX (N=101)	PBO (N=51)	ROX (N=NR)	DAR (N=NR)
CV Mortality	**n (%)**		0 (0)	0 (0)	NR	
	Time to Event	**HR (95% CI), p-value**	NR			
No data reported for the following outcomes: MACE*, MACE+†, MI, stroke, heart failure, unstable angina, heart failure requiring hospitalization, unstable angina requiring hospitalization						

95% CI: 95% confidence interval, CV: cardiovascular, DAR: darbepoetin alfa, HR: hazard ratio, MI: myocardial infarction, MACE: major adverse cardiovascular event, N: total number, n: number, NR: not reported, PBO: placebo, ROX: roxadustat

*Defined as all-cause mortality (not CV mortality), MI, or stroke.

†MACE+: defined as MACE or unstable angina requiring hospitalization or congestive heart failure requiring hospitalization.

Evidence Table 13. CV Safety – Phase II Trials

Trial			FGCL-SM4592-017[41]		FGCL-4592-047[42]			1517-CL-0303[43]			
Arm			Pooled ROX (N=88)*	PBO (N=28)	ROX, Low-Dose (N=30)	ROX, High-Dose (N=31)	PBO (N=30)	ROX, Low-Dose (N=27)	ROX, Middle-Dose (N=27)	ROX High-Dose (N=26)	PBO (N=27)
CV Mortality	n (%)		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Time to Event	HR (95% CI), p-value	NR		NR		---	NR			---
MACE†	n (%)		NR		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Time to Event	HR (95% CI), p-value			NR		---	NR			---
MI	n (%)		NR		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Time to Event	HR (95% CI), p-value			NR		---	NR			---
Stroke	n (%)		NR		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Time to Event	HR (95% CI), p-value			NR		---	NR			---
Heart Failure	n (%)		1 (1.1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3.7)	0 (0)	0 (0)	1 (3.7)
	Time to Event	HR (95% CI), p-value	NR		NR		---	NR			---
Unstable Angina	n (%)				0 (0)	0 (0)	1 (3.3)	NR			---
	Time to Event	HR (95% CI), p-value			NR		---				
Data on the following outcomes not reported: MACE+, heart failure requiring hospitalization, unstable angina requiring hospitalization											

95% CI: 95% confidence interval, CV: cardiovascular, Diff.: difference, HR: hazard ratio, MI: myocardial infarction, MACE: major adverse cardiovascular event, n: number, N: total number, NR: not reported, PBO: placebo, ROX: roxadustat

*Data for individual arms not reported.

†Defined as all-cause mortality (not CV mortality), MI, or stroke.

Evidence Table 14. Safety – Key Trials

Trial		ALPS[20,22,23,39]		ANDES[18,22]		DOLOMITES[21]		OLYMPUS[19,22,26,49]	
Arm		ROX (N=391)	PBO (N=203)	ROX (N=611)	PBO (N=305)	ROX (n=323)	DAR (N=293)	ROX (N=1384)	PBO (N=1377)
Timepoint		On treatment* + 28 Days		On treatment† + 28 Days		36 Weeks		On treatment‡ + 28 Days	
Any AEs, n (%)		ERP100PY: 476.7	ERP100PY: 514.7	ERP100PY: 554.4	ERP100PY: 594.5	NR		1243 (89.8)	1216 (88.3)
Any TEAEs, n (%)		343 (87.7)	176 (86.7)	564 (92.3)	273 (89.5)	296 (91.6)	271 (92.5)	NR	
Drug-Related TEAEs, n (%)		81 (20.7)	27 (13.3)	NR		NR		NR	
Serious AEs, n (%)		ERP100PY: 78.9	ERP100PY: 97.1	NR	NR	NR		795 (57.4)	749 (54.4)
Serious TEAEs, n (%)		241 (61.6)	115 (56.7)	ERP100PY: 74.2	ERP100PY: 66.0	209 (64.7)	181 (61.8)	NR	
D/C due to AEs, n (%)		23 (5.9)¥	8 (3.9)¥	85 (13.8)§	30 (9.8)§	25 (7.7)¥	11 (3.8)¥	79 (5.7)	52 (3.8)
All-Cause Mortality	n (%)	45 (11.5)¤	20 (9.9)¤	58 (9.5)#	24 (7.9)#	29 (9)**	31 (10.6)**	284 (20.5)††	245 (17.8)††
	HR (95% CI), p-value	0.96 (0.53, 1.74), 0.902**		NR		0.83 (0.50, 1.38), 0.467		NR	
Hospitalization, days/PEY (SD)		26.5 (NR)#	31.9 (NR)#	NR		NR		NR	
ESRD, n (%)		135 (34.5)	62 (30.5)	67 (11.0)	18 (5.9)	108 (33.4)	106 (36.2)	290 (21.0)	282 (20.5)
Decline in eGFR, n (%)		43 (11.0)	23 (11.3)	NR		55 (17)	49 (16.7)	NR	
Pulmonary Embolism, n (%)		NR		NR		NR		NR	
Hypertension, n (%)		87 (22.3)	28 (13.8)	95 (15.5)	27 (8.9)	NR		159 (11.5)	125 (9.1)

95% CI: 95% confidence interval, AE: adverse event, D/C: discontinuation, DAR: darbepoetin alfa, eGFR: estimated glomerular filtration rate, ERP100Y: event rate per 100 person years, HR: hazard ratio, n: number, N: total number, NR: not reported, PBO: placebo, PEY: patient exposure years, ROX: roxadustat, SAE: serious adverse event, TEAE: treatment-emergent adverse event

*Up to 2 years.

†Up to 3 years.

‡Up to 4.5 years.

#Timeframe not reported.

¥Due to TEAE.

§Due to AE or death.

¤We note disagreement among sources.

**Safety-emergent period.

††Up to and including the end of study visit or date of last contact or withdrawal of consent.

Evidence Table 15. Safety – Other Phase III Trials

Trial		FGCL-4592-808[40]		1517-CL-0310[38]	
Arm		ROX (N=101)	PBO (N=51)	ROX (N=NR)	DAR (N=NR)
Timepoint		8 weeks		NR	
Any AEs, n (%)		69 (68.0)	38 (75.0)		
Any TEAEs, n (%)		NR			
Drug-Related TEAEs, n (%)		NR			
Serious AEs, n (%)		9 (9.0)	6 (12.0)		
Serious TEAEs, n (%)		NR			
D/C due to AEs, n (%)		6 (5.9)	5 (9.6)		
All-Cause Mortality	**n (%)**	0 (0)	0 (0)		
	HR (95% CI), p-value	NR			
Hospitalization, n (%)		NR			
End Stage Renal Disease, n (%)		1 (1.0)	0 (0)		
Decline in eGFR, n (%)		NR			
Pulmonary Embolism, n (%)		NR			
Hypertension, n (%)		6 (6.0)	2 (4.0)		

95% CI: 95% confidence interval, AE: adverse event, DAR: darbepoetin alfa, D/C: discontinuation, eGFR: estimated glomerular filtration rate, HR: hazard ratio, n: number, N: total number, NR: not reported, PBO: placebo, ROX: roxadustat, SAE: serious adverse event, TEAE: treatment-emergent adverse event

Evidence Table 16. Safety – Phase II Trials

Trial		FGCL-SM4592-017[41]		FGCL-4592-047[42]				1517-CL-0303[43]			
Arm		Pooled ROX (N=88)*	PBO (N=28)	ROX, Low-Dose (N=30)	ROX, High-Dose (N=31)	Pooled ROX (N=61)	PBO (N=30)	ROX, Low-Dose (N=27)	ROX, Middle-Dose (N=26)	ROX High-Dose (N=27)	PBO (N=27)
Timepoint		12 weeks		8 weeks				24 weeks			
Any AEs, n (%)		NR		NR				NR			
Any TEAEs, n (%)		52 (59.1)	13 (46.4)	NR		36 (59.0)	19 (63.0)	20 (74.1)	23 (88.5)	20 (74.1)	19 (70.4)
Drug-Related TEAEs, n (%)		NR		17 (57.0)	19 (61.0)	36 (59.0)	19 (63.0)	10 (37.0)	4 (15.4)	5 (18.5)	4 (14.8)
Serious AEs, n (%)		4 (5.0)	1 (4.0)	NR				NR			
Serious TEAEs, n (%)		NR		NR		8 (13.1)	4 (13.3)	6 (22.2)	2 (7.7)	3 (11.1)	2 (7.4)
D/C due to AEs, n (%)		2 (2.3)	1 (3.6)	2 (6.7)	0 (0)	2 (3.3)	1 (3.3)	8 (29.6)	0 (0)	3 (11.1)	2 (7.4)
All-Cause Mortality	n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	HR (95% CI), p-value	NR		NR			---	NR			---
Hospitalization, n (%)		NR		NR				NR			
End Stage Renal Disease, n (%)		NR		NR				NR			
Decline in eGFR, n (%)		NR		1 (3.3)	0 (0)	1 (1.6)	0 (0)	4 (14.8)	0 (0)	1 (3.7)	1 (3.7)
Pulmonary Embolism, n (%)		NR		NR				NR			
Hypertension, n (%)		2 (2.3)	NR	1 (3.0)	3 (10.0)	4 (7.0)	0 (0)	NR			

95% CI: 95% confidence interval, AE: adverse event, D/C: discontinuation, DAR: darbepoetin alfa, eGFR: estimated glomerular filtration rate, HR: hazard ratio, n: number, N: total number, NR: not reported, PBO: placebo, ROX: roxadustat, SAE: serious adverse event, TEAE: treatment-emergent adverse event

*Data for individual arms not reported.

Evidence Table 17. Study Design

Trial (NCT) & Author	Design & Follow-Up Duration	Location	N	Arms	Key Inclusion Criteria	Key Exclusion Criteria	Definitions
HIMALAYAS **NCT02052310**[24]	Phase III, open-label, active-controlled, randomized trial Follow-Up: – Treatment period: 52 weeks to 4 years – Post-treatment follow-up: 4 weeks	Global	1043	**Roxadustat (N=522)** Weight-based starting dose – ≤70 kg: 70 mg TIW – 70-160 kg: 100 mg TIW **Epoetin alfa (N=521)** – HD: dosed per USPI or SmPC – PD dosed per USPI or SmPC or local SOC	– Receiving HD or PD for 2 weeks to 4 months – Hb ≤10.0 g/dL – Ferritin ≥100 ng/mL and TSAT ≥20%	– ESA treatment within 12 weeks – Total duration of prior effective ESA use must be ≤3 weeks within preceding 12 weeks at the time consent is obtained (US only) – IV iron supplementation within 10 days – Use of iron-binding medications within 4 weeks – Blood transfusion within 8 weeks – Congestive heart failure – MI, stroke, or blood clots within a major vessel within 12 weeks – Uncontrolled hypertension – Active cancer – Known and untreated damage to the retina from diabetes	**Hb Response:** Hb ≥11 g/dL and a Hb increase from baseline of ≥1 g/dL for baseline Hb >8 g/dL or ≥2 g/dL for baseline Hb ≤8 g/dL
ROCKIES **NCT02174731**[26]	Phase III, open-label, active-controlled, randomized trial Follow-Up: – Treatment period: up to 4 years – Post-treatment follow-up: 4 weeks	Global	2133	**Roxadustat (N=1,068)** ESA-experienced: – Epoetin alfa or beta <5000 IU/week or darbepoetin alfa <25 µg/week or methoxy polyethylene glycol-epoetin beta <80 µg/month: 70 mg TIW – Epoetin alfa or beta 5000-8000 IU/week or darbepoetin alfa 25-40 µg/week or methoxy polyethylene glycol-epoetin beta 80-120 µg/month: 100 mg TIW – Epoetin alfa or beta >8000-16000 IU/week or darbepoetin alfa 40-80 µg/week or methoxy polyethylene glycol-	– Receiving HD or PD for ≥2 weeks – Hb <12 g/dL if on ESA or Hb <10 g/dL if not on ESA for ≥4 weeks or methoxy polyethylene glycol-epoetin beta for ≥8 weeks before the first visit – Ferritin ≥100 ng/mL – TSAT ≥20%	– Blood transfusion during the screening period – NYHA class III or IV congestive heart failure at enrollment – MI, acute coronary syndrome, stroke, seizure, or a thrombotic/ thromboembolic event within 12 weeks – Uncontrolled hypertension – History malignancy – Known and untreated retinal vein occlusion or known and untreated proliferative diabetic retinopathy (risk for retinal vein thrombosis)	**Hb Response:** Hb ≥ 11.0 g/dL and Hb increase from baseline by ≥ 1.0 g/dL, for subjects with baseline Hb > 8.0 g/dL; or Hb increase from baseline by ≥ 2.0 g/dL, for subjects with baseline Hb ≤ 8.0 g/dL and Proportion of total time of Hb within the interval of 10-12 g/dL from week 28 to week 52

Trial (NCT) & Author	Design & Follow-Up Duration	Location	N	Arms	Key Inclusion Criteria	Key Exclusion Criteria	Definitions
				epoetin beta 120-200 µg/month: 150 mg TIW – Epoetin alfa or beta >16000 IU/week or darbepoetin alfa >80 µg/week or methoxy polyethylene glycol-epoetin beta >200 µg/month: 200 mg TIW ESA-naïve: – 45-70 kg: 70 mg TIW – >70-160 kg: 100 mg TIW **Epoetin alfa (N=1,065)** ESA-naïve: – 50 IU/kg TIW ESA-experienced: – Dosed at approximately the same average weekly dose prior to randomization			
SIERRAS **NCT02273726**[22]	Phase III, open-label, active controlled, randomized trial Follow-Up: – Treatment period: 52 weeks to 3 years – Post-treatment follow-up	US and Latin America	741	**Roxadustat (N=370)** ESA-experienced: – Epoetin alfa, beta, theta, zeta, delta, or omega <5000 IU/week or darbepoetin alfa <25 µg/week or methoxy polyethylene glycol-epoetin beta <80 µg/month: 70 mg TIW – Epoetin alfa, beta, theta, zeta, delta, or omega 5000-8000 IU/week or darbepoetin alfa 25-40 µg/week or methoxy polyethylene glycol-	– Receiving HD or PD – Ferritin ≥100 ng/mL – TSAT ≥20% Stable DD-CKD: – Receiving ESA treatment ≥8 weeks – Hb 9.0-12.0 g/dL ID-CKD: – Receiving ESA treatment ≥4 weeks – Hb 8.5-12.0 g/dL	– Blood transfusion within 8 weeks prior to randomization – NYHA class III or IV congestive heart failure – MI, stroke, seizure, or a thrombotic/thromboembolic event within 12 weeks prior to study participation – History of malignancy, except for following: cancers determined to be cured or in remission for ≥5 years, curatively resected basal cell or squamous cell skin cancers, cervical cancer in situ, or resected colonic polyps	

Trial (NCT) & Author	Design & Follow-Up Duration	Location	N	Arms	Key Inclusion Criteria	Key Exclusion Criteria	Definitions
	period: 4 weeks			epoetin beta 80-120 µg/month: 100 mg TIW – Epoetin alfa, beta, theta, zeta, delta, or omega: >8000-16000 IU/week or darbepoetin alfa 40-80 µg/week or methoxy polyethylene glycol-epoetin beta 120-200 µg/month: 150 mg TIW – Epoetin alfa, beta, theta, zeta, delta, or omega: >16000 IU/week or darbepoetin alfa >80 µg/week or methoxy polyethylene glycol-epoetin beta >200 µg/month: 200 mg TIW **Epoetin alfa (N=371)**			
PYRENEES **NCT02278341[25]**	Phase III, open-label, active-controlled, randomized trial Follow-Up: – Treatment period: 52 weeks to 104 weeks – Post-treatment follow-up period: 4 weeks	Europe	836	**Roxadustat (N=415)** Dosed per patient's average weekly dose of EPO or DAR within 4 weeks prior to randomization – EPO <8000 IU/week or darbepoetin alfa <40 µ/week: 100 mg TIW – EPO 8000-16000 IU/week or darbepoetin alfa 40-80 µ/week: 150 mg TIW – EPO >16000 IU/week or darbepoetin alfa >80 µ/week: 200 mg TIW **ESA (N=421)** Dosed at approximately the same average weekly dose prior to randomization	– Receiving stable HD, HDF, or PD with the same mode of dialysis ≥4 months – IV or SC epoetin or IV or SC darbepoetin alfa treatment for ≥8 weeks prior to randomization with stable weekly doses during 4 weeks prior to randomization – Hb 9.5–12 g/dL – Ferritin ≥100 ng/mL – TSAT ≥20%	– Blood transfusion within 8 weeks – MI, acute coronary syndrome, stroke, seizure, or a thrombotic/ thrombo-embolic event within 12 weeks – History of malignancy	**Hb Response:** mean Hb during weeks 28 to 36 within the target range of 10.0 to 12.0 g/dL without having received rescue therapy within 6 weeks prior to and during this 8-week evaluation period.

Trial (NCT) & Author	Design & Follow-Up Duration	Location	N	Arms	Key Inclusion Criteria	Key Exclusion Criteria	Definitions
				– DAR (n=163) – EPO (n=258)			
FGCL-4592-806 **NCT02652806** **Chen 2019[40]**	Phase III, open-label, active controlled, randomized trial Follow-Up: 26 weeks	China	305	**Roxadustat (N=204)** – 45-60 kg: 100 mg TIW – ≥60 kg: 120 mg TIW **Epoetin alfa (N=101)** Dose was based on epoetin alfa dose prior to randomization	– 18-75 years of age – ESKD – Receiving adequate HD or PD ≥16 weeks – Receiving stable doses of epoetin alfa ≥6 weeks – Hb 9.0-12.0 g/dL	– IV iron supplementation during the screening period – Blood transfusion within 12 weeks – NYHA class III or IV congestive heart failure – MI, acute coronary syndrome, stroke, seizure, or a thromboembolic event within 52 weeks – History of malignancy – Uncontrolled hypertension	**Hb Response:** Hb not <1.0 g/dL below baseline
1517-CL-0307 **NCT02952092** **Akizawa 2020[44]**	Phase III, parallel-arm, double-blind, active controlled, randomized trial Follow-Up: – 24 weeks	Japan	303	**Roxadustat (N=151)** – 70 or 100 mg BIW or TIW **Darbepoetin alfa (N=152)** Dose was based on rHuEPO or darbepoetin alfa dose prior to randomization	– ≥ 20 years of age – CKD diagnosis and receiving HD TIW >12 weeks prior to the pre-screening – Receiving IV rHuEPO or darbepoetin alfa >8 weeks prior to pre-screening – Hb 10.0-12.0 g/dL – Either TSAT ≥20% or serum ferritin ≥100 ng/mL	– Blood transfusion or a surgical procedure considered to promote anemia and ophthalmological surgery within 4 weeks – NYHA class III or higher congestive heart failure – History of hospitalization for treatment of stroke, MI, or pulmonary embolism with 12 weeks – History of malignancies – Untreated retinal neovascular lesion; macular edema – Uncontrolled hypertension – Anemia not related to CKD	
FGCL-4592-040 **NCT01147666** **Provenzano 2016[45]**	Phase II, open-label, active controlled, randomized, dose-ranging trial Follow-Up:	US	144	**Part 1: Roxadustat (n=41)** – Roxadustat 1.0 mg/kg TIW – Roxadustat 1.5 mg/kg TIW – Roxadustat 1.8 mg/kg TIW – Roxadustat 2.0 mg/kg TIW **Part 1: Epoetin alfa (N=13)** Continuation of rerandomization dose	– 18 – 75 years of age – ESRD and receiving HD ≥4 months – Hb 9.0 to 13.5 g/dL for 8 weeks – Stable epoetin alfa dose ≤450 U/kg/ week for 4 weeks – ALT and AST ≤2x ULN	– Received any ESA other than IV EPO within 12 weeks; received IV EPO within 3 days – IV iron supplementation within 2 weeks – RBC transfusion within 12 weeks – NYHA Class III or IV congestive heart failure – MI or ACS within 3 months	**Hb Response:** – Part 1: Hb change ≥0.5 g/dL – Part 2: Mean Hb level ≥11.0 g/dL during the last 4 weeks of treatment

Trial (NCT) & Author	Design & Follow-Up Duration	Location	N	Arms	Key Inclusion Criteria	Key Exclusion Criteria	Definitions
	– TX period (part 1): 6 weeks – TX period (part 2): 19 weeks – Post-TX follow-up period (part 1): 8 weeks – Post-TX follow-up period (part 2): 4 weeks			**Part 2: Roxadustat (N=67)** – Roxadustat 1.8 mg/kg TIW – Roxadustat 1.8 mg/kg TIW – 45-60 kg: Roxadustat 70-100-150 mg TIW – >60-90 kg: Roxadustat 70-120-200 mg TIW – Roxadustat 2.0 mg/kg TIW – >90-140 kg: Roxadustat: 70-120-200 mg TIW **Part 2: Epoetin alfa (n=23)**		– Thromboembolic event within 12 weeks – History of malignancy	
FGCL-4592-048 **NCT01596855** **Chen 2017**	Phase II, open-label, active-controlled, randomized trial Follow-Up: 7 weeks	China	87	**Roxadustat (N=65)** – Low dose (40-60 kg) (n=22) : 1.1 to 1.8 mg/kg TIW – Medium dose (>60-80 kg) (n=21): 1.5 to 2.3 mg/kg TIW – High dose (>80-100 kg) (n=22): 1.7 to 2.3 mg/kg TIW **Epoetin alfa (N=22)** Continuation of pre-randomization dose and schedule	– Ages 18 – 75 years of age – CKD diagnosis and receiving HD three times weekly TIW for ≥4 months – Receiving stable doses of epoetin alfa for 7 weeks prior – Mean Hb between ≥9.0 and ≤12.0 g/dL	– Received any ESA other than epoetin alfa within 12 weeks; received epoetin alfa within 3-7 days – IV iron supplementation during the screening visit – RBC transfusion within 12 weeks – NYHA Class III or IV congestive heart failure – MI or ACS within 3 months – Thromboembolic event within 12 weeks – History of malignancy	**Hb Response:** Hb maintained at no more than 0.5 g/dL below mean baseline value (weeks 4-6)
1517-CL-0304[46] **NCT01888445**	Phase II, 4-arm, multicenter, double-blind (arms 1-3), and open-label (arm 4),	Japan	130	**Roxadustat (N=98)** – 50 mg TIW – 70 mg TIW – 100 mg TIW **Darbepoetin alfa (N=32)** – 20µg QW	– Receiving HD ≥12 weeks – Patients who are receiving ESA for ≥8 weeks – Hb ≥10.0 g/dL	– Congestive heart failure (NYHA classification III or higher) – History of hospitalization for stroke, MI, or lung infarction within 24 weeks	**Hb response:** patient whose Hb is ≥10.0 g/dL and who achieve an increase in Hb of ≥ 1.0 g/dL

Trial (NCT) & Author	Design & Follow-Up Duration	Location	N	Arms	Key Inclusion Criteria	Key Exclusion Criteria	Definitions
	active controlled, randomized trial <u>Follow-Up:</u> – Fixed-dose period: 6 weeks – Titration period: 18 weeks – Post-treatment follow-up period: 4 weeks						

ACS: acute coronary syndrome, DAR: darbepoetin alfa, dL: deciliter, EPO: epoetin alfa, ESA: erythropoiesis stimulating agent, g: gram, Hb: hemoglobin, HD: hemodialysis, HDF: hemodiafiltration, IU: international unit, IV: intravenous, kg: kilogram, µg: microgram, mg: milligram, MI: myocardial infarction, mL: milliliter, N: total number, ng: nanogram, NYHA: New York Heart Association, PD: peritoneal dialysis, QW: weekly, RBC: red blood cell, rHuEPO: recombinant human erythropoietin, SC: subcutaneous, SOC: standard of care, TIW: thrice weekly, TSAT: transferrin saturation, TX: treatment

Evidence Table 18. Baseline Characteristics – Key Trials

Trial		HIMALAYAS[22,24]		ROCKIES[22,26,100]		SIERRAS[22]		PYRENEES[22,25,99]	
Arm		ROX (N=522)	EPO (N=521)	ROX (N=1068)	EPO (N=1065)	ROX (N=370)	EPO (N=371)	ROX (N=414)	ESA* (N=420)
Age, mean years (SD)		53.8 (14.7)	54.3 (14.6)	53.5 (15.3)	54.5 (15.0)	57.6 (NR)	58.4 (NR)	61.0 (13.8)	61.8 (13.4)
Male, n (%)		309 (59.2)	307 (58.9)	625 (59.3)	626 (59.3)	NR		245 (59.2)	235 (56.0)
White, n (%)		478 (91.6)	471 (90.4)	607 (56.8)	580 (56.7)	165 (44.6)	184 (49.6)	405 (97.8)	407 (96.9)
Hemodialysis, n (%)		469 (89.8)	462 (88.7)	953 (89.2)	947 (88.9)	NR		NR	
Peritoneal Dialysis, n (%)		53 (10.2)	58 (11.1)	113 (10.6)	118 (11.1)	NR		NR	
Dialysis Vintage ≤4 Months, n (%)		522 (100)	521 (100)	202 (18.9)	215 (20.2)	36 (9.7)	35 (9.5)	0 (0)	0 (0)
Hb, mean g/dL (SD)		8.43 (1.04)	8.46 (0.96)	9.99 (1.20)	10.02 (1.20)	10.25 (NR)	10.25 (NR)	10.75 (0.62)	10.78 (0.62)
Transferrin Saturation, mean % (SD)		27.02 (9.30)	27.56 (8.90)	NR		33.60 (10.1)	33.60 (10.0)	NR	
Ferritin, mean ng/mL (SD)		441.00 (337.00)	437.00 (311.40)	NR		1000.20 (459.1)	960.80	NR	
CRP, mg/L	Mean (SD)	NR		NR		NR		NR	
	>ULN†, n (%)	228 (43.7)	226 (43.4)	NR		189 (51.1)	177 (47.7)	NR	
Data not reported for the following baseline characteristics: hepcidin, transferrin, soluble transferrin receptor, serum iron, total iron binding capacity, iron status – replete, total cholesterol, LDL-cholesterol, HDL-cholesterol									

CRP: C-reactive protein, dL: deciliter, EPO: epoetin alfa, ESA: erythropoiesis-stimulating agent, g: gram, L: liter, mL: milliliter, N: total number, n: number, ng: nanogram, NR: not reported, PBO: placebo, ROX: roxadustat, SD: standard deviation, ULN: upper limit of normal

*Includes both epoetin alfa and darbepoetin alfa.

†Defined as 4.9 mg/L.

Evidence Table 19. Baseline Characteristics – Other Phase III Trials

Trial		FGCL-4592-806[40]		1517-CL-0307[44]	
Arm		ROX (N=204)	EPO (N=100)	ROX (N=150)	DAR (N=151)
Age, mean years (SD)		47.6 (11.7)	51.0 (11.8)	64.6 (11.7)	64.9 (10.1)
Male, n (%)		126 (61.8)	58 (58.0)	101 (67.3)	107 (70.9)
White, n (%)		0 (0)[#]	0 (0)[#]	0 (0)[#]	0 (0)[#]
Hemodialysis, n (%)		182 (89.2)	89 (89.0)	150 (100)	151(100)
Peritoneal Dialysis, n(%)		22 (10.8)	11 (11.0)	0 (0)	0 (0)
Dialysis Vintage ≤4 Months, n (%)		0 (0)	0 (0)	0 (0)	0 (0)
Hb, mean g/dL (SD)		10.4 (0.7)	10.5 (0.7)	11.02 (0.56)	11.01 (0.60)
Hepcidin, mean ng/mL (SD)		180.70 (SE: 136.80)	148.30 (SE: 104.2)	26.44 (21.50)	24.45 (21.00)
Transferrin, mean g/L (SD)		1.89 (0.46)	1.91 (0.39)	1.80 (0.33)	1.81 (0.30)
Transferrin Saturation, mean % (SD)		33.80 (16.6)	30.00 (13.80)	28.28 (11.70)	29.04 (10.18)
Serum Iron, mean µg/dL (SD)		NR	NR	67.60 (28.49)[†]	70.39 (25.14)[†]
Total Iron Binding Capacity, mean µg/dL (SD)		264.80 (63.69)[†]	269.83 (50.28)[†]	NR	NR
Ferritin, mean ng/mL (SD)		498.5 (487.4)	420.1 (406.8)	102.31 (83.45)	96.28 (75.14)
Iron Status - Replete[‡], n (%)		NR	NR	44 (29.3)	48 (31.8)
CRP, mg/L	Mean (SD)	NR	NR	1.32 (2.41)	1.46 (2.29)
	>ULN*, n (%)	46 (22.5)	20 (20.0)	NR	NR
Total Cholesterol, mean mg/dL (SD)		168.2 (42.9)	165.1 (41.4)	NR	NR
LDL-C, mean mg/dL (SD)		95.1 (34.8)	90.1 (29.4)	NR	NR
HDL-C, mean mg/dL (SD)		43.3 (12.0)	44.5 (15.1)	NR	NR
Data for the following baseline characteristics not reported: Soluble transferrin receptor					

CRP: C-reactive protein, DAR: darbepoetin alfa, dL: deciliter, EPO: epoetin alfa, g: gram, HDL-C: high-density lipoprotein cholesterol, L: liter, LDL-C: low-density lipoprotein cholesterol, mg: milligram, mL: milliliter, N: total number, n: number, ng: nanogram, NR: not reported, PBO: placebo, ROX: roxadustat, SD: standard deviation, SE: standard error, ULN: upper limit of normal

*Defined as 4.9 mg/L.

†Converted from µmol/L to µg/dL.

‡Ferritin ≥100 ng/ml and TSAT ≥20%.

#All patients were Asian.

Evidence Table 20. Baseline Characteristics – Phase II Trials

Trial	FGCL-4592-040[45]				FGCL-4592-048[42]				1517-CL-0304[46]			
Arm	**Pooled ROX (Pt 1) (N=41)**	**EPO (Pt 1) (N=13)**	**Pooled ROX (Pt 2) (N=67)**	**EPO (Pt 2), (N=23)**	**ROX, Low (N=25)**	**ROX, Medium (N=24)**	**ROX, High (N=25)**	**EPO (N=22)**	**ROX 50 mg (N=32)**	**ROX 70 mg (N=32)**	**ROX 100 mg (N=31)**	**DAR (N=32)**
Age, mean years (SD)	55.8 (13.4)	59.5 (10.1)	56.9 (12.1)	57.0 (11.6)	49.9 (14.7)	50.2 (9.3)	49.8 (13.5)	53.8 (10.0)	62.3 (8.7)	62.4 (9.7)	61.7 (9.8)	60.0 (7.9)
Male, n (%)	27 (66.0)	9 (69.0)	45 (67.0)	14 (61.0)	16 (64.0)	14 (58.3)	15 (60.0)	13 (59.1)	22 (68.8)	24 (75.0)	25 (80.6)	22 (68.8)
White, n (%)	27 (66.0)	5 (39.0)	35 (52.0)	6 (26.0)	0 (0)‡	0 (0)‡	0 (0)‡	0 (0)‡	0 (0)‡	0 (0)‡	0 (0)‡	0 (0)‡
Hemodialysis, n (%)	41 (100)	13 (100)	67 (100)	23 (100)	25 (100)	24 (100)	25 (100)	22 (100)	32 (100)	32 (100)	31 (100)	32 (100)
Peritoneal Dialysis, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Dialysis Vintage ≤4 Months, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Hb, mean g/dL (SD)	11.3 (0.6)	11.5 (0.6)	11.2 (0.7)	11.2 (1.0)	10.9 (0.7)	10.7 (0.8)	10.8 (0.6)	10.6 (1.0)	8.92 (0.38)	8.79 (0.42)	8.80 (0.60)¤	8.80 (0.51)
Hepcidin, mean ng/mL (SD)	236.6 (159.7)	279.3 (137.6)	327.1 (178.8)	298.7 (123.1)	157.0 (124.0)	198.4 (113.1)	174.4 (124.0)	209.0 (127.1)	NR			
Transferrin, mean g/L (SD)	NR	NR	NR	NR	1.88 (0.39)#	1.94 (0.36)#	1.86 (0.58)#	1.87 (0.35)#	1.70 (0.27)	1.77 (0.39)	1.65 (0.25)¤	1.78 (0.28)
TSAT, mean % (SD)	30.10 (8.20)	31.50 (11.50)	29.20 (10.20)	28.60 (14.60)	29.8 (16.7)	32.1 (18.2)	32.8 (15.8)	34.1 (14.6)	42.37 (16.78)	44.76 (15.85)	43.87 (15.79)¤	37.26 (16.06)
Soluble Transferrin Receptor, mean mg/L (SD)	2.74 (0.86)	3.25 (0.76)	4.03 (1.81)	3.69 (0.93)	3.90 (1.80)	3.40 (1.20)	3.40 (1.10)	2.90 (1.20)	0.78 (0.33)§	0.78 (0.36)§	0.88 (0.43)§	1.02 (0.5)§
Serum Iron, Mean µg/dL (SD)	70.40 (20.90)	70.20 (27.20)	66.40 (20.60)	63.30 (32.00)	68.0 (35.6)	75.5 (39.5)	71.9 (21)	79.0 (31.9)	92.18 (29.61)¥	103.35 (42.46)¥	94.41 (32.96)¥¤	85.47 (35.75)¥
TIBC, mean µg/dL (SD)	210.80 (41.30)	200.80 (30.90)	199.7 (34.00)	202.10 (26.70)	218.0 (46.0)	221.0 (41.0)	213.0 (61.0)	214.0 (38.0)	225.14 (28.49)¥	234.08 (46.37)¥	218.99 (26.82)¥¤	234.64 (32.96)¥

Trial		FGCL-4592-040[45]				FGCL-4592-048[42]				1517-CL-0304[46]			
Arm		Pooled ROX (Pt 1) (N=41)	EPO (Pt 1) (N=13)	Pooled ROX (Pt 2) (N=67)	EPO (Pt 2), (N=23)	ROX, Low (N=25)	ROX, Medium (N=24)	ROX, High (N=25)	EPO (N=22)	ROX 50 mg (N=32)	ROX 70 mg (N=32)	ROX 100 mg (N=31)	DAR (N=32)
Ferritin, mean ng/mL (SD)		917.30 (458.0)	929.70 (494.2)	826.8 (484.5)	1106.60 (642.1)	380.0 (345.0)	488.0 (372.0)	485.0 (391.0)	458.0 (361.0)	191.52 (209.26)	186.70 (220.10)	192.52 (119.74)¤	156.99 (102.49)
CRP, mg/L	Mean (SD)	NR				4.04 (5.30)	6.65 (9.83)	1.94 (3.04)	3.00 (4.70)	NR			
	>ULN*, n (%)					NR							
Total Cholesterol, mean mg/dL (SD)		NR				172.0 (38.0)	169.0 (32.0)	172.0 (36.0)	158.0 (28.0)	NR			
LDL-C, mean mg/dL (SD)		NR				103.0 (31.0)	100.0 (30.0)	103.0 (24.0)	91.0 (24.0)	NR			
HDL-C, mean mg/dL (SD)		NR				39.0 (12.0)	39.0 (14.0)	39.0 (15.0)	41.0 (14.0)	NR			
Data for the following baseline characteristics not reported: iron status – replete**													

CRP: C-reactive protein, DAR: darbepoetin alfa, dL: deciliter, EPO: epoetin alfa, ESA: erythropoiesis-stimulating agent, g: gram, L: liter, µg: microgram, mL: milliliter, N: total number, n: number, ng: nanogram, NR: not reported, PBO: placebo, Pt.: part, ROX: Roxadustat, SD: standard deviation, TIBC: total iron binding capacity, ULN: upper limit of normal

*Defined as 4.9 mg/L.

†N of patients for whom data was available.

‡All patients were Asian.

#Converted from mg/dL to g/L.

¥Converted from µmol/L to µg/dL.

§Converted from nmol/L to mg/L.

¤n=30.

**Defined as ≥100 ng/mL and TSAT ≥20%.

Evidence Table 21. Efficacy Outcomes – Key Trials

Trials			HIMALAYAS[22,24]		ROCKIES[22,26,100]		SIERRAS[22]		PYRENEES[22,25,99]	
Arm			ROX	EPO	ROX	EPO	ROX	EPO	ROX	ESA[¥]
Change in Hb, g/dL	Timepoint		Average of 28 to 52 Weeks							
	N		522	521	1003	1016	370	371	413	420
	LSM (SE)		Mean: 2.57 (NR)	Mean: 2.36 (NR)	0.77 (0.04)	0.68 (0.04)	Mean: 0.39 (SD: 0.95)	Mean: -0.09 (SD: 0.90)	0.36 (95% CI: 0.29, 0.44)	0.19 (95% CI: 0.21, 0.26)
	Between Group Diff.	LSM (95% CI), p-value	0.18 (0.08, 0.29), 0.0005		0.09 (0.01, 0.18), 0.036		0.48 (0.37, 0.59), <0.0001		0.171 (0.08, 0.26), <0.001	
Hb Response	Timepoint		24 Weeks		Average of 28 to 52 Weeks		Average of 28 to 52 Weeks		Average of 28 to 36 weeks	
	N		522	521	896	941	370	371	386	397
	n (%)		460 (88.2)	440 (84.4)	708 (79.0)	715 (76.0)	245 (66.1)	217 (58.6)	325 (84.2)	327 (82.4)
	Between Group Diff.	LSM (95% CI), p-value	3.5 (-0.7, 7.7), NR		0.03 (0.00, 0.05), <0.045		NR		2.3 (-2.9, 7.6), NR	
Use of Rescue Therapy	Timepoint		NR		NR		NR		Up to 104 weeks	
	N								413	420
	n (%)								53 (12.8)	60 (14.4)
	Time to Event	HR (95% CI), p-value							0.98 (0.66, 1.46), NR	
Use of Blood Transfusion	Timepoint		During Treatment[#]		During Treatment Period[#] + 28 days		During Treatment**		104 weeks	
	N		522	521	1048	1053	370	371	413	420
	Time to First Transfusion, months (95% CI)		NR		Ep100PY: 6.0	Ep100PY: 7.2	NR		11.4 (8.0, 14.9)	14.4 (10.8, 18.0)

Trials			HIMALAYAS[22,24]		ROCKIES[22,26,100]		SIERRAS[22]		PYRENEES[22,25,99]	
Arm			ROX	EPO	ROX	EPO	ROX	EPO	ROX	ESA[¥]
	n (%)				NR	NR	46 (12.5)	78 (21.0)	NR	
	Time to Event	HR (95% CI), p-value	1.26 (0.79, 2.02), 0.328		0.83 (0.64, 1.07), 0.151		0.67 (NR), <0.0037		0.87 (0.57, 1.31), NR	
Use of IV Iron	Timepoint		Average of 45 to 52 Weeks		Week 36 to End of Study		36 Weeks		Week 53 to 104	
	N		522	513	885	920	370	371	413	420
	Mean Monthly Use, mg (SD)		46.9 (8.1)*	71.5 (7.5)*	58.7 (236.1)	91.4 (225.6)	17.1 (53.4)	37.0 (106.8)	LSM: 49.5 (95% CI: 31.0, 67.9)	LSM: 98.1 (95% CI: 81.1, 115.2)
	n (%)		NR		NR		NR		NR	
	Time to Event	HR (95% CI), p-value	NR, 000028		NR, <0.0001		NR, =0.00091		LSM: -35.1 (-51.8, -18.4), <0.001[†]	
Change in Hepcidin, ng/mL	Timepoint		NR		24 Weeks		52 Weeks		up to 108 weeks	
	N				608	625	370	371	280	320
	Mean (SD)				-44.99 (NR)	-16.77 (NR)	-95.53 (148.27)	-66.66 (141.61)	-27.19 (52.17)	-17.66 (51.69)
	Between Group Diff.	Mean (95% CI), p-value			NR, <0.001		NR, 0.0662		NR	
Change in TSAT, %	Timepoint		52 Weeks		Week 24 to End of Treatment		52 Weeks		108 Weeks	
	N		522	513	866	939	370	371	283	321
	Mean (SD)		-2.10 (0.70)*	-2.30 (0.50)*	-1.92 (NR)	-2.44 (NR)	–7.96 (13.7)	–9.78 (13.07)	-5.47 (16.63)	-3.76 (17.81)
	Between Group Diff.	Mean (95% CI), p-value	NR		-0.52 (NR), 0.287		NR, 0.0341		NR	
Change in Soluble	Timepoint		NR		Week 24 to End of Treatment		NR		NR	
	N				874	946				

Trials			HIMALAYAS[22,24]		ROCKIES[22,26,100]		SIERRAS[22]		PYRENEES[22,25,99]	
Arm			ROX	EPO	ROX	EPO	ROX	EPO	ROX	ESA[¥]
Transferrin Receptor, mg/L	Mean (SD)				0.35 (NR)[††]	–0.02 (NR)[††]				
	Between Group Diff.	Mean (95% CI), p-value			NR, <0.001					
Change in Serum iron, µg/dL	Timepoint		NR		Week 24 to End of Treatment		52 Weeks		NR	
	N				877	946	370	3		
	Mean (SD)				6.58 (NR)	-5.54 (NR)	-2.12 (36.12)	-15.64 (28.3)		
	Between Group Diff.	Mean (95% CI), p-value			NR, <0.001		NR, <0.0001			
Change in Ferritin, ng/mL	Timepoint		NR		Week 24 to End of Treatment		52 Weeks		End of Study	
	N				875	946	370	371	290	323
	Mean (SD)				-104.47 (NR)	-41.18 (NR)	–4.26 (3.40)[§]	–3.94 (3.39)[§]	pmol/L: -554.53 (910.01)	pmol/L: -166.94 (2035.26)
	Between Group Diff.	Mean (95% CI), p-value			NR, <0.001		NR, 0.1356		NR	
Change in Total Cholesterol, mg/dL	Timepoint		NR		NR		Weeks 12 to 28		104 Weeks	
	N						370	371	247	307
	Mean (SD)						-23.9	-1.7	-0.90 (1.05)	-0.28 (1.00)
	Between Group Diff.	Mean (95% CI), p-value					NR		NR	
	Timepoint		NR		24 Weeks		Average of Weeks 12 to 28		Average of Weeks 12 to 28	
	N				902	937	370	371	394	412

Trials			HIMALAYAS[22,24]		ROCKIES[22,26,100]		SIERRAS[22]		PYRENEES[22,25,99]	
Arm			ROX	EPO	ROX	EPO	ROX	EPO	ROX	ESA[¥]
Change in LDL-C, mg/dL	Mean (95% CI)				-14.67 (SD: 1.00)[‡]	-1.93 (SD: 1.00)[‡]	-13.70 (NR)	1.23 (NR)	LSM: -17.72 (20.07, -15.44)	LSM: -3.17 (-5.33, -1.00)
	Between Group Diff.	LSM (95% CI), p-value			-12.74 (-15.05, -10.42)[‡], <0.001		–14.67 (–17.64, –11.70), <0.0001		-14.67 (-17.37, -11.58), <0.001	
Data on the following outcomes not reported: Use of ESA treatment, transferrin, total iron binding capacity, HDL-C										

95% CI: 95% confidence interval, Diff.: difference, dL: deciliter, EPO: epoetin alfa, Ep100PY: event per 100 person years, ESA: erythropoiesis-stimulating agent, g: gram, Hb: hemoglobin, HDL-C: high-density lipoprotein cholesterol, IV: intravenous, L: liter, LDL-C: low-density lipoprotein cholesterol, HR: hazard ratio, LSM: least squares mean, µg: microgram, mg: milligram, mL: milliliter, N: total number, n: number, ng: nanogram, NR: not reported, ns: not significant, PBO: placebo, ROX: roxadustat, SD: standard deviation, SE: standard error, TSAT: transferrin saturation

*Data are digitized and should be interpreted with caution.

†LSM difference in monthly IV iron use.

‡Converted to mg/dL.

§Converted to ng/mL.

¥Includes both epoetin alfa and darbepoetin alfa.

#Up to 4 years.

**Up to 3 years.

††Converted to mg/L.

Evidence Table 22. Efficacy Outcomes – Other Phase III Trials

Trials			FGCL-4592-806[103]		1517-CL-0307[44]	
Arm			ROX (N=204)	EPO (N=100)	ROX (N=114)	DAR (N=131)
Change in Hb, g/dL	Timepoint		Average of 23 to 27 Weeks		Average of 18 to 24 Weeks	
	LSM (SE)		Mean: 0.70 (SD: 1.10)	Mean: 0.50 (SD: 1.00)	-0.04 (95% CI: -0.16, 0.08)	-0.03 (95% CI: -0.14, 0.09)
	Between Group Difference	LSM (95%C), p-value	0.20 (-0.02, 0.50), NR		-0.02 (-0.18, 0.15), NR	
Hb Response	Timepoint		23 to 27 Weeks		NR	
	n (%)		189 (92.5)	93 (92.5)		
	Between Group Diff.	LSM (95% CI), p-value	0.2 (-7.1, 7.6), NR			
Use of Rescue Therapy	Timepoint		27 Weeks		NR	
	n (%)		3 (1.5)	1 (1.0)		
	Time to Event	HR (95% CI), p-value	1.68 (0.18, 16.19), NR			
Use of ESA Treatment	Timepoint		Up to and including 2 days after trial-drug discontinuation		NR	
	n (%)		2 (1.0)	NR		
	Time to Event	HR (95% CI), p-value	NR			
Change in Hepcidin, ng/mL	Timepoint		27 Weeks		24 Weeks	
	N		155	90	150	151
	Mean (SD)		-30.20 (SE: 113.30)	-2.30 (SE: 130.70)	2.31 (27.28)	-0.60 (27.06)
	Between Group Diff.	LSM (95% CI), p-value	NR		NR	
Change in Transferrin, g/L	Timepoint		27 Weeks		24 Weeks	
	N		160	94	150	151
	Mean (SD)		LSM: 0.38 (SE: 0.05)	LSM: -0.05 (SE: 0.04)	0.42 (0.39)	0.11 (0.29)
	Between Group Diff.	LSM (95% CI), p-value	0.43 (0.32, 0.53), NR		NR	
Change in TSAT, %	Timepoint		27 Weeks		24 Weeks	
	N		159	93	150	151

Trials			FGCL-4592-806[103]		1517-CL-0307[44]	
Arm			ROX (N=204)	EPO (N=100)	ROX (N=114)	DAR (N=131)
	Mean (SD)		LSM: -4.50 (SE: 1.20)	LSM: -8.70 (SE: 1.00)	-1.09 (13.84)	-2.44 (13.83)
	Between Group Diff.	LSM (95% CI), p-value	4.20 (1.50, 6.90), NR		NR	
Change in Soluble Transferrin Receptor, mg/L	Timepoint		NR		24 weeks	
	N				150	151
	Mean (SD)				0.14 (0.90)†	0.36 (0.96)†
	Between Group Diff.	Mean (95% CI), p-value			NR	
Change in Serum iron, µg/dL	Timepoint		27 Weeks		24 Weeks	
	N		160	94	150	151
	Mean (SD)		LSM: 3.35 (SE: 3.91)*	LSM: -21.79 (SE: 2.79)*	6.70 (35.75)*	-5.03 (30.73)*
	Between Group Diff.	LSM (95% CI), p-value	24.58 (16.76, 32.96)*, NR		NR	
Change in Total Iron Binding Capacity, µg/dL	N		159	93	150	151
	Timepoint		27 weeks		24 weeks	
	Mean (SD)		LSM: 53.07 (SE: 6.70)*	LSM: -6.70 (SE: 6.15)*	43.58 (45.25)*	8.94 (31.84)*
	Between Group Diff.	LSM (95% CI), p-value	59.78 (45.25, 74.30)*, NR		NR	
Change in Ferritin, ng/mL	Timepoint		27 Weeks		24 weeks	
	N		160	94	150	151
	Mean (SD)		LSM: -99.00 (SE: 19.00)	LSM: -133.00 (SE: 21.00)	-3.98 (78.41)	18.75 (64.64)
	Between Group Diff.	LSM (95% CI), p-value	35.00 (-12.00, 82.00), NR		NR	
Change in Total Cholesterol, mg/dL	Timepoint		27 Weeks		NR	
	N		158	94		
	Mean (SD)		-26.70 (30.60)	3.99 (NR)‡		
	Between Group Diff.	Mean (95% CI), p-value	-22.00 (-29.00, 16.00), NR			

Trials			FGCL-4592-806[103]		1517-CL-0307[44]	
Arm			ROX (N=204)	EPO (N=100)	ROX (N=114)	DAR (N=131)
Change in LDL-C, mg/dL	Timepoint		27 Weeks		NR	
	N		204	101		
	Mean (SD)		-24.00 (24.70)	1.53 (NR)‡		
	Between Group Diff.	LSM (95% CI), p-value	-18.00 (-23.00, -13.00), NR			
Change in HDL-C, mg/dL	Timepoint		27 Weeks		NR	
	N		204	101		
	Mean (SD)		4.3 (7.7)	2.67 (NR)‡		
	Between Group Diff.	Mean (95% CI), p-value	-2.00 (-4.00, -0.10), NR			
No data reported on the following outcomes: Use of blood transfusion, use of IV iron						

95% CI: 95% confidence interval, DAR: darbepoetin alfa, Diff.: difference, dL: deciliter, EPO: epoetin alfa, Ep100PY: event per 100 person years, ESA: erythropoiesis stimulating agent, g: gram, Hb: hemoglobin, HR: hazard ratio, IV: intravenous, L: liter, LSM: least squares mean, µg: microgram, mL: milliliter, N: total number, n: number, ng: nanogram, NR: not reported, ns: not significant, ROX: Roxadustat, SD: standard deviation, SE: standard error, TSAT: transferrin saturation

*Converted from µmol/L to µg/dL.

†Converted from nmol/L to mg/L.

‡Data are digitized and should be interpreted with caution.

Evidence Table 23. Efficacy Outcomes – Phase II Trials

Trials			FGCL-4592-040[45]				FGCL-4592-048[42]					1517-CL-0304[46]			
Arm			Pooled ROX (Pt 1)	EPO (Pt 1)	Pooled ROX (Pt 2)	EPO (Pt 2)	ROX Low	ROX Medium	ROX High	Pooled ROX	EPO	ROX, 50 mg	ROX, 70 mg	ROX, 100 mg	DAR
Change in Hb, g/dL	Timepoint		6 Weeks		19 Weeks		6 Weeks					Average of 18 to 24 Weeks			
	N		41	13	61	22	22	18	20	60	22	17	24	22	27
	Mean (SD)		LSM (SE): 0.30 (NR)	LSM (SE): -1.00 (NR)	LSM (SE): -0.50 (0.20)	LSM (SE): -0.50 (0.30)	0.11 (1.00)	1.10 (1.00)	1.42 (1.21)	0.84 (1.18)	0.17 (0.96)	1.33 (0.81)	1.37 (0.93)	1.57 (0.98)	1.42 (1.02)
	Between Group Diff.	LSM (95% CI) p-value	NR		-0.03 (-0.39, 0.33), NR		NR					NR			
Hb Response	Timepoint		4 Weeks		15 – 19 Weeks		6 Weeks					24 Weeks			
	N		33	9	61	22	22	18	20	60	22	15	22	19	24
	n (%)		23 (67.9)	3 (33.3)	31 (51.0)	8 (36.0)	13 (59.1)	16 (88.9)	20 (100.0)	49 (81.7)	11 (50.0)	9 (60.0)	15 (68.2)	14 (73.7)	15 (62.5)
	Between Group Diff.	LSM (95% CI), p-value	NR, 0.063		NR		NR, 0.53	NR, 0.008	NR, 0.0003	NR, 0.004	--	NR	NR	NR	---
Use of Rescue Therapy	Timepoint		NR				6 Weeks					NR			
	N						22	18	20	60	22				
	n (%)						0 (0)	0 (0)	0 (0)	0 (0)	0 (0)				
	Time to Event	HR (95% CI), p-value					NR								
Use of Blood Transfusion	Timepoint		NR				6 Weeks					NR			
	N						22	18	20	60	22				
	Time to First Transfusion						NR	NR	NR	NR	NR				

Trials			FGCL-4592-040[45]				FGCL-4592-048[42]					1517-CL-0304[46]			
Arm			Pooled ROX (Pt 1)	EPO (Pt 1)	Pooled ROX (Pt 2)	EPO (Pt 2)	ROX Low	ROX Medium	ROX High	Pooled ROX	EPO	ROX, 50 mg	ROX, 70 mg	ROX, 100 mg	DAR
	n (%)						0 (0)	0 (0)	0 (0)	0 (0)	0 (0)				
	Time to Event	HR (95% CI), p-value					NR								
Use of IV Iron	Timepoint		6 Weeks		19 Weeks		6 Weeks								
	N		41	13	67	23	22	18	20	60	22				
	Mean monthly use, mg (SD)		NR	NR	NR	NR									
	n (%)		5 (12.0)	2 (15.0)	2 (3.0)	3 (13.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)				
	Time to Event	HR (95% CI) p-value	NR		NR, 0.1		NR								
Use of ESA Treatment	N						22	18	20	60	22				
	Timepoint						6 Weeks								
	n (%)						0 (0)	0 (0)	0 (0)	0 (0)	0 (0)				
	Time to Event	HR (95% CI) p-value	NR				NR								
Change in Hepcidin, ng/mL	Timepoint		6 Weeks		19 Weeks		6 Weeks								
	N		33	9	61	22	22	18	20	60	22				
	Mean (SD)		-39.2 (226.9)	-6.5 (140.1)	-60.4 (187.8)	35.6 (123.4)	-25.70 (108.68)	-86.00 (109.41)	-102.70 (80.40)	-70.20 (104.19)	-77.90 (75.18)				
	Between Group Diff.	Mean (95% CI), p-value	NR 0.3		NR 0.04		NR 0.13	NR 0.65	NR 0.005	NR 0.71	--				
	N		NR				22	18	20	60	22				

Trials			FGCL-4592-040[45]				FGCL-4592-048[42]					1517-CL-0304[46]			
Arm			Pooled ROX (Pt 1)	EPO (Pt 1)	Pooled ROX (Pt 2)	EPO (Pt 2)	ROX Low	ROX Medium	ROX High	Pooled ROX	EPO	ROX, 50 mg	ROX, 70 mg	ROX, 100 mg	DAR
Change in Transferrin, g/L	Timepoint						6 weeks								
	Mean (SD)						0.40 (0.38)*	0.50 (0.44)*	0.59 (0.41)*	0.50 (0.41)*	0.03 (0.16)*				
	Between Group Diff.	Mean (95% CI) p-value					NR, 0.0004	NR, <0.0001	NR, <0.0001	NR, <0.0001	--				
Change in TSAT, %	Timepoint		6 Weeks		19 Weeks		6 Weeks					NR			
	N		33	9	61	22	22	18	20	60	22				
	Mean (SD)		-2.50 (13.7)	-7.00 (4.1)	-2.40 (18.9)	-5.30 (12.5)	-3.77 (21.41)	-8.98 (14.73)	-4.87 (17.22)	-5.77 (17.93)	-8.29 (10.46)				
	Between Group Diff.	Mean (95% CI) p-value	NR, 0.4		NR, 0.4		NR, 0.8	NR, 0.98	NR, 0.57	NR, 0.74	--				
Change in Soluble Transferrin Receptor, mg/L	Timepoint		6 Weeks		19 Weeks		6 Weeks					NR			
	N		33	9	61	22	22	18	20	60	22				
	Mean (SD)		0.69 (1.54)	0.20 (0.73)	0.86 (2.69)	20.33 (1.52)	0.51 (2.38)	0.52 (0.95)	2.05 (1.81)	1.05 (1.95)	0.88 (1.19)				
	Between Group Diff.	Mean (95% CI) p-value	NR, 0.6		NR, 0.2		NR, 0.59	NR, 0.48	NR, 0.011	NR, 0.52	--				
Change in Serum iron, µg/dL	Timepoint		6 Weeks		19 Weeks		6 Weeks					NR			
	N		33	9	61	22	22	18	20	60	22				
	Mean (SD)		7.10 (33.9)	-14.00 (11.1)	5.2 (42.2)	-5.5 (30.2)	3.20 (55.8)	-3.30 (34.5)	8.90 (35.9)	3.10 (43.0)	-18.90 (26.7)				
	Between Group Diff.	Mean (95% CI) p-value	NR, 0.07		NR, 0.1		NR, ns	NR, ns	NR, <0.05	NR, ns	--				
Change in Total Iron	Timepoint		6 Weeks		19 Weeks		6 Weeks					NR			
	N		33	9	61	22	22	18	20	60	22				

Trials			FGCL-4592-040[45]				FGCL-4592-048[42]					1517-CL-0304[46]			
Arm			Pooled ROX (Pt 1)	EPO (Pt 1)	Pooled ROX (Pt 2)	EPO (Pt 2)	ROX Low	ROX Medium	ROX High	Pooled ROX	EPO	ROX, 50 mg	ROX, 70 mg	ROX, 100 mg	DAR
Binding Capacity, µg/dL	Mean (SD)		51.0 (27.4)	5.0 (26.4)	37.6 (41.4)	25.6 (47.3)	41.5 (37.5)	50.6 (46.0)	59.1 (40.5)	50.5 (41.3)	0.5 (17.4)				
	Between Group Diff.	Mean (95% CI) p-value	NR, <0.001		NR, 0.3		NR, 0.0001	NR, <0.0001	NR, <0.0001	NR, <0.0001	--				
Change in Ferritin, ng/mL	Timepoint		6 Weeks		19 Weeks		6 Weeks					NR			
	N		33	9	61	22	22	18	20	60	22				
	Mean (SD)		-185.5 (190.5)	-146.5 (180.7)	-201.1 (334.4)	-211.6 (445.2)	21.0 (186.0)	-149.0 (145.0)	-162.0 (179.0)	-95.0 (189.0)	-70.0 (157.0)				
	Between Group Diff.	Mean (95% CI), p-value	NR, 0.5		NR, 0.8		NR, 0.06	NR, 0.13	NR, 0.04	NR, 0.52	--				
Change in Total Cholesterol, mg/dL	Timepoint		6 Weeks		19 Weeks		6 Weeks					NR			
	N		NR		67	23	22	18	20	60	22				
	Mean (SD)				30.93 (NR)†	0.72 (NR)†	-11.10 (31.31)	-13.10 (31.64)	-15.80 (48.63)	-13.30 (37.55)	18.30 (24.32)				
	Between Group Diff.	Mean (95% CI) p-value			NR, ns		NR, 0.0045	NR, 0.0045	NR, 0.0012	NR, 0.0003	--				
Change in LDL-C, mg/dL	Timepoint		NR				6 Weeks					NR			
	N						22	18	20	60	22				
	Mean (SD)						-25.0 (20.2)	-23.4 (20.6)	-25.8 (27.6)	-24.8 (22.6)	-5.0 (15.3)				
	Between Group Diff.	Mean (95% CI), p-value					NR 0.008	NR 0.013	NR 0.007	NR 0.001	--				
	Timepoint		NR				6 Weeks					NR			

Trials			FGCL-4592-040[45]				FGCL-4592-048[42]					1517-CL-0304[46]			
Arm			Pooled ROX (Pt 1)	EPO (Pt 1)	Pooled ROX (Pt 2)	EPO (Pt 2)	ROX Low	ROX Medium	ROX High	Pooled ROX	EPO	ROX, 50 mg	ROX, 70 mg	ROX, 100 mg	DAR
Change in HDL-C, mg/dL	N						22	18	20	60	22				
	Mean (SD)						-8.2 (7.8)	-6.6 (8.4)	-6.6 (12.5)	-7.2 (9.6)	-1.9 (7.4)				
	Between Group Diff.	Mean (95% CI) p-value					NR, 0.005	NR, 0.034	NR, 0.014	NR, 0.002	--				

95% CI: 95% confidence interval, DAR: darbepoetin alfa, Diff.: difference, dL: deciliter, EPO: epoetin alfa, Ep100PY: event per 100 person years, ESA: erythropoiesis-stimulating agent, g: gram, Hb: hemoglobin, HDL-C: high-density lipoprotein cholesterol, HR: hazard ratio, IV: intravenous, L: liter, LDL-C: low-density lipoprotein cholesterol, LSM: least squares mean, µg: microgram, mg: milligram, mL: milliliter, N: total number, n: number, ng: nanogram, NR: not reported, ns: not significant, PBO: placebo, pt.: part, ROX: roxadustat, SD: standard deviation, SE: standard error, TSAT: transferrin saturation, ULN: upper limit of normal

*Converted from mg/dL to mg/L.

†Data are digitized and should be interpreted with caution.

Evidence Table 24. Changes in Hb – Subgroups

Trial			HIMALAYAS[22,24]								ROCKIES[22,26,100]		SIERRAS[22]	
Population			Iron Replete*		Iron Deplete†		CRP ≤ULN‡		CRP >ULN‡		CRP >ULN#		CRP >ULN#	
Arm			ROX (N=NR)	EPO (N=NR)	ROX (N=NR)	EPO (N=NR)	ROX (N=NR)	EPO (N=NR)	ROX (N=NR)	EPO (N=NR)	ROX (N=280)	EPO (N=301)	ROX (N=NR)	EPO (N=NR)
Timepoint			During Treatment¥ + 28 Days								Average of Weeks 28 to 52		Average of Weeks 18 to 24	
Change in Hb, g/dL	Mean (SD)		NR		NR		NR		NR		0.80 (NR)	0.59 (NR)	0.61 (NR)	-0.03 (NR)
	Btw. Group Diff.	Mean (95% CI), p-value	0.15 (0.03, 0.27), NR		0.31 (0.08, 0.54), NR		0.18 (0.05, 0.31), NR		0.19 (0.02, 0.36), NR		NR, 0.012		0.69 (0.50, 0.87), <0.0001	

95% CI: 95% confidence interval, btw.: between, CRP: c-reactive protein, Diff.: difference, dL: deciliter, EPO: epoetin alfa, g: gram, Hb: hemoglobin, N: total number, NR: not reported, ULN: upper limit of normal, ROX: roxadustat, SD: standard deviation

*Ferritin ≥100 ng/ml and TSAT ≥20%.

†Ferritin <100 ng/mL or TSAT <20%.

‡Defined as 4.9 mg/L.

#Defined as 5.0 mg/L.

¥Up to 4 years.

Evidence Table 25. Patient Reported Outcomes – Key Trials

Trials			HIMALAYAS		ROCKIES		SIERRAS		PYRENEES[100]	
Arm			ROX	EPO	ROX	EPO	ROX	EPO	ROX (N=415)	ESA* (N=421)
Timepoint			Weeks 12-28							
Change in SF-36 Physical Functioning, Points	N		NR		NR		NR		376	391
	Mean (95% CI)								0.05 (-0.64, 0.74)	-0.16 (-0.83, 0.51)
	Between Group Diff.	LSM (95% CI), p-value							0.21 (-0.65, 1.06), NR	
Change in SF-36 Vitality, Points	N		NR		NR		NR		377	391
	Mean (95% CI)								0.46 (-0.33, 1.25)	-0.40 (-1.17, 0.37)
	Between Group Diff.	LSM (95% CI), p-value							0.86 (-0.12, 1.83), NR	
Change in SF-36 Physical Component Summary, Points	N		NR		NR		NR		384	404
	Mean (95% CI)								0.56 (-0.03, 1.15)	0.04 (-0.53, 0.61)
	Between Group Difference	LSM (95% CI), p-value							0.52 (-0.21, 1.25), NR	
Change in FACT-An Anemia, Points	N		NR		NR		NR		384	403
	LSM (95% CI)								0.53 (-0.49, 1.55)	0.36 (-0.62, 1.34)
	Between Group Diff.	LSM (95% CI), p-value							0.17 (-1.08, 1.43), 0.788	
Change in FACT-An Total Score, Points	N		NR		NR		NR		383	403
	LSM (95% CI)								-0.39 (-2.47, 1.68)	-0.29 (-2.28, 1.70)
	Between Group Diff.	LSM (95% CI), p-value							-0.11 (-2.67, 2.46), 0.936	
Change in EQ-5D 5L, VAS	N		NR		NR		NR		385	401
	LSM (SD)								3.04 (14.91)	2.74 (14.78)
	Between Group Diff.	LSM (95% CI), p-value							NR	NR
Improvement in PGIC, %	Timepoint		NR		NR		NR		104 Weeks	
	N								413	420
	n (%)								254 (61.6)	215 (51.3)
	Between Group Diff.	LSM (95% CI), p-value							NR	NR
Data for other subscales not reported										

95% CI: 95% confidence interval, Diff.: difference, EQ-5D-5L: European Quality of Life Questionnaire-5 Dimensions-5 Levels, EPO: epoetin alfa, ESA: erythropoiesis-stimulating agent, FACT-An: Functional Assessment of Cancer Therapy – Anemia, LS: least squares, N: total number, n: number, NR: not reported, ns: not significant, PGIC: patients' Global Impression of Change, ROX: roxadustat, SD: standard deviation, SF-36: 36-Item Short Form Survey, VAS: visual analog scale

*Includes both epoetin alfa and darbepoetin alfa.

Evidence Table 26. CV Safety – Key Trials

Trials			HIMALAYAS[22,24]		ROCKIES[100]		SIERRAS[22]		PYRENEES[25,99]	
Arm			ROX (N=522)	EPO (N=521)	ROX (N=1048)	EPO (N=1053)	ROX (N=370)	EPO (N=370)	ROX (N=414)	ESA* (N=420)
Timepoint			Treatment + 28 days post treatment							
CV Mortality	n (%)		NR		NR		NR		1 (0.2)	1 (0.2)
	Time to Event	HR (95% CI), p-value							NR	
Myocardial Infarction	n (%)		NR		53 (5.0)§	47 (4.5)§	34 (9.2)¶	26 (7.0)¶	10 (2.4)§	17 (4.0)§
	Time to Event	HR (95% CI), p-value			NR		NR		NR	
Stroke	n (%)		NR		16 (1.5)#	18 (1.7)#	NR		1 (0.2)**	2 (0.5)**
	Time to Event	HR (95% CI), p-value			NR				NR	
Heart Failure	n (%)		NR		48 (4.6)††	49 (4.7)††	30 (8.1)‡‡	33 (8.9)‡‡	17 (4.1)††	12 (2.9)††
	Time to Event	HR (95% CI), p-value			NR		NR		NR	
Unstable Angina	n (%)		NR		5 (0.5)	6 (0.6)	NR		0 (0)	2 (0.5)
	Time to Event	HR (95% CI) p-value			NR				NR	
Data for the following outcomes not reported: MACE†, MACE+‡, heart failure requiring hospitalization, unstable angina requiring hospitalization										

95% CI: 95% confidence interval, CV: cardiovascular, EPO: epoetin alfa, ESA: erythropoiesis-stimulating agent, HR: hazard ratio, MACE: major adverse cardiovascular event, N: total number, n: number, NR: not reported, ROX: roxadustat

*Includes both epoetin alfa and darbepoetin alfa.

†Defined as all-cause mortality (not cardiovascular mortality), MI, or stroke.

‡Defined as MACE or unstable angina requiring hospitalization or congestive heart failure requiring hospitalization.

§Includes acute myocardial infarction and myocardial infarction.

¶Acute MI.

#Includes brain stem stroke, hemorrhagic stroke, ischemic stroke, embolic stroke, lacunar stroke.

**Includes hemorrhagic stroke and ischemic stroke.

††Includes cardiac failure, cardiac failure acute, cardiac failure chronic, and cardiac failure congestive.

‡‡Cardiac failure congestive.

Evidence Table 27. CV Safety – Other Phase III Trials

Trials			FGCL-4592-806[103]		1517-CL-0307[44]	
Arm			ROX (N=204)	EPO (N=100)	ROX (N=150)	DAR (N=152)
Timepoint			27 Weeks		24 Weeks	
Cardiovascular Mortality	n (%)		0 (0)	0 (0)	NR	
	Time to Event	HR (95% CI), p-value	NR			
MI	n (%)		1 (0.5)#	0 (0)#	1 (0.7)#	0 (0)#
	Time to Event	HR (95% CI), p-value	NR		NR	
Stroke	n (%)		NR		1 (0.7)¥	0 (0)¥
	Time to Event	HR (95% CI), p-value			NR	
Heart Failure	n (%)		3 (1.5)	0 (0)	1 (0.7)	1 (0.7)
	Time to Event	HR (95% CI), p-value	NR		NR	
Data on the following outcomes not reported: MACE†, MACE+‡, unstable angina, Heart Failure Requiring Hospitalization, Unstable Angina Requiring Hospitalization						

95% CI: 95% confidence interval, DAR: darbepoetin alfa, EPO: epoetin alfa, HR: hazard ratio, MACE: major adverse cardiovascular event, N: total number, n: number, NR: not reported, ROX: roxadustat

†Defined as all-cause mortality (not CV mortality), MI, or stroke.

‡Defined as MACE or unstable angina requiring hospitalization or congestive heart failure requiring hospitalization.

#Acute MI.

¥Cerebral infarction.

Evidence Table 28. CV Safety – Phase II Trials

Trials			FGCL-4592-040[45]		FGCL-4592-048[42]				1517-CL-0304[46]			
Arm			All Pooled ROX (N=108)	All Pooled EPO (N=36)	ROX, Low (N=25)	ROX, Medium (N=24)	ROX, High (N=25)	EPO (N=22)	ROX 50 mg (N=33)	ROX 70 mg (N=32)	ROX 100 mg (N=32)	DAR (N=32)
Timepoint			Weeks 6 and 19		Week 6				24 weeks			
CV Mortality	n (%)		NR		0 (0)	0 (0)	0 (0)	0 (0)	NR			
	Time to Event	HR (95% CI), p-value			NR			---				
MACE*	n (%)		NR		0 (0)	0 (0)	0 (0)	0 (0)	NR			
	Time to Event	HR (95% CI), p-value			NR			---				
MACE+†	n (%)		NR		NR				NR			
	Time to Event	HR (95% CI), p-value										
MI	n (%)		0 (0)	1 (3.0)	0 (0)	0 (0)	0 (0)	0 (0)	NR			
	Between Group Diff.	HR (95% CI), p-value	NR		NR							
Stroke	n (%)		NR		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3.1)‡	0 (0)	0 (0)
	Time to Event	HR (95% CI), p-value			NR				NR			
Heart Failure	n (%)		1 (0.9)	1 (3.0)	NR				1 (3.0)	0 (0)	2 (6.3)	0 (0)
	Time to Event	HR (95% CI), p-value	NR						NR			
Data on the following outcomes not reported: unstable angina, heart failure requiring hospitalization, unstable angina requiring hospitalization												

95% CI: 95% confidence interval, DAR: darbepoetin alfa, EPO: epoetin alfa, HR: hazard ratio, MACE: major adverse cardiovascular event, N: total number, n: number, NR: not reported, ROX: roxadustat

*Definition NR.

†Defined as MACE or unstable angina requiring hospitalization or congestive heart failure requiring hospitalization.

‡Cerebral infarction.

Evidence Table 29. Safety – Key Trials

Trials			HIMALAYAS[22,24]		ROCKIES[22,26,100]		SIERRAS[22]		PYRENEES[22,25,99]	
Arm			ROX (N=522)	EPO (N=517)	ROX (N=1048)	EPO (N=1053)	ROX (N=370)	EPO (N=370)	ROX (N=414)	ESA* (N=420)
Timepoint			Treatment + 28 days post treatment							
Any AE, n (%)			NR		891 (85.0)	890 (84.5)	NR		77 (86.7)	361 (86.0)
Any TEAE, n (%)			450 (86.2)	441 (85.3)	NR		339 (91.6)	338 (91.4)	359 (86.7)	361 (86.0)
TEAEs Related to Study Drug, n (%)			NR		15 (7.4)	1 (1.0)	NR		33 (8.0)	10 (2.4)
Any Serious AE, n (%)			NR		604 (57.6)	605 (57.5)	NR		NR	
Serious TEAEs, n (%)			234 (44.8)	218 (42.2)	NR		242 (65.4)	248 (67.0)	210 (50.7)	189 (45.0)
D/C due to AE, n (%)			29 (5.6)	22 (4.2)	57 (5.4)	26 (2.5)	NR	NR	35 (8.5)	16 (3.8)
All-Cause Mortality	n (%)		63 (12.1)	59 (11.4)	167 (15.9)	187 (17.8)	62 (16.8)	58 (15.7)	78 (18.8)	59 (14.0)
	Time to Event	HR (95% CI), p-value	NR		NR		NR		NR	
Hospitalization, n (%)			NR		NR		NR		4 (0.9)†	4 (0.9)
Pulmonary Embolism, n (%)			NR		6 (0.6)	8 (0.8)	NR		4 (1.0)	1 (0.2)
Hypertension, n (%)			99 (19.0)	88 (17.0)	92 (8.8)	94 (8.9)	62 (16.8)	47 (12.7)	74 (17.9)	79 (18.8)
Pulmonary Hypertension, n (%)			NR		0 (0)	2 (0.2)	NR		2 (0.5)	1 (0.2)

95% CI: 95% confidence interval, AE: adverse event, D/C: discontinuation, EPO: epoetin alfa, ESA: erythropoiesis-stimulating agent, HR: hazard ratio, N: total number, n: number, NR: not reported, ROX: roxadustat, EAE: treatment-emergent adverse event

*Includes both epoetin alfa and darbepoetin alfa.

†N=413.

Evidence Table 30. Safety – Other Phase III Trials

Trials			FGCL-4592-806[103]		1517-CL-0307[44]	
Arm			ROX (N=204)	EPO (N=100)	ROX (N=150)	DAR (N=152)
Timepoint			27 weeks		24 weeks	
Any AE, n (%)			NR		NR	
Any TEAE, n (%)			159 (77.9)	63 (63.0)	NR	
TEAEs Related to Study Drug, n (%)			96 (47.1)	38 (38.0)	129 (86.0)	126 (82.9)
Any Serious AE, n (%)			NR		NR	
Serious TEAEs, n (%)			29 (14.2)	10 (10.0)	31 (20.7)	22 (14.5)
D/C due to TEAE, n (%)			17 (8.4)	1 (1.0)	13 (8.7)	8 (5.3)
All-Cause Mortality	n (%)		0 (0)	0 (0)	2 (1.3)	0 (0)
	Time to Event	HR (95% CI), p-value	NR		NR	
Hospitalization, n (%)			NR		NR	
Pulmonary embolism, n (%)			NR		NR	
Hypertension, n (%)			25 (12.3)	16 (16.0)	NR	
Pulmonary Hypertension, n (%)			NR		NR	

95% CI: 95% confidence interval, AE: adverse event, DAR: darbepoetin alfa, D/C: discontinuation, EPO: epoetin alfa, ESA: erythropoiesis-stimulating agent, HR: hazard ratio, N: total number, n: number, NR: not reported, ROX: roxadustat, TEAE: treatment-emergent adverse event

Evidence Table 31. Safety – Phase II Trials

Trials			FGCL-4592-040[45]		FGCL-4592-048[42]				1517-CL-0304[46]			
Arm			All pooled ROX (N=108)	All pooled EPO (N=36)	ROX, low (N=25)	ROX, medium (N=24)	ROX, high (N=25)	EPO (N=22)	ROX 50 mg (N=33)	ROX 70 mg (N=32)	ROX 100 mg (N=33)	DAR (N=32)
Timepoint			6 and 19 weeks		6 weeks				24 weeks			
Any AE, n (%)			69 (63.9)	22 (61.0)	NR				NR			
Any TEAE, n (%)			NR		10 (40.0)	13 (54.0)	9 (36.0)	4 (18.0)	24 (72.7)	26 (81.3)	27 (84.4)	25 (78.1)
TEAEs Related to Study Drug, n (%)			NR		NR				8 (24.2)	7 (21.9)	12 (37.5)	2 (6.3)
Any Serious AE, n (%)			26 (24.1)	6 (17.0)	0 (0)	0 (0)	0 (0)	0 (0)	NR			
Serious TEAEs, n (%)			NR		0 (0)	0 (0)	0 (0)	0 (0)	4 (12.1)	7 (21.9)	4 (12.5)	2 (6.3)
D/C due to TEAE, n (%)			3 (4.5)*	0 (0)	0 (0)	1 (4.8)	0 (0)	0 (0)	2 (6.1)	2 (6.3)	3 (9.4)	0 (0)
All-Cause Mortality	n (%)		3 (4.5)†	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3.0)	0 (0)	0 (0)	0 (0)
	Time to Event	HR (95% CI), p-value	NR		NR				NR			
Hospitalization, n (%)			NR		NR				NR			
Pulmonary Embolism, n (%)			NR		NR				NR			
Hypertension, n (%)			NR		0 (0)	2 (8.0)	1 (4.0)	1 (5.0)	NR			
Pulmonary Hypertension, n (%)			NR		NR				NR			

95% CI: 95% confidence interval, AE: adverse event, DAR: darbepoetin alfa, D/C: discontinuation, EPO: epoetin alfa, ESA: erythropoiesis stimulating agent, HR: hazard ratio, N: total number, n: number, NR: not reported, ROX: roxadustat, TEAE: treatment-emergent adverse event

*Occurred during Part 1.

†Occurred during Part 2.

Evidence Table 32. Baseline Characteristics

Trials		DI-CKD *(ALPS, ANDES, OLYMPUS)*[17,22,97,98]		DD-CKD *(HIMALAYAS, ROCKIES, SIERRAS)*[17,22,97,98]	
Arm		**ROX (N=2391)**	**PBO (N=1886)**	**ROX (N=1943)**	**EPO (N=1947)**
Age, mean years (SD)		61.9 (14.1)	62.7 (14.0)	54.3 (14.9)	55.1 (14.6)
Male, n (%)		974 (40.7)	832 (44.1)	1121 (57.7)	1148 (59.0)
White, n (%)		1134 (47.4)	892 (47.3)	1177 (60.6)	1182 (60.7)
History of Cardiac, Cerebrovascular, or Thromboembolic Disease; n (%)		886 (37.1)	695 (36.9)	940 (48.7)	923 (47.9)
Hemodialysis, n (%)		N/A		1750 (90.7)	1740 (90.2)
Peritoneal Dialysis, n (%)		N/A		177 (9.2)	188 (9.8)
Dialysis Vintage ≤4 Months, n (%)		N/A		760 (39.4)	770 (39.9)
Hb, mean g/dL (SD)		9.10 (0.74)	9.10 (0.73)	9.63 (1.30)	9.67 (1.30)
Hepcidin, mean ng/mL (SD)		114.79 (NR)	122.04 (NR)	240.58 (NR)	236.90 (NR)
Transferrin, mean mg/L (SD)		2.40 (NR)†	2.37 (NR)†	2.16 (NR)†	2.15 (NR)†
Transferrin Saturation, mean % (SD)		28.18 (NR)	28.98 (NR)	33.00 (12.74)	32.70 (12.40)
Ferritin, mean ng/mL (SD)		262.92 (NR)	257.88 (NR)	608.64 (466.50)	602.15 (469.60)
Iron Status, Replete‡, n (%)		1433 (59.9)	1127 (59.8)	1690 (87.0)	1692 (86.9)
Serum Iron, mean µg/dL (SD)		65.71 (NR)	66.74 (NR)	70.21 (NR)	69.73 (NR)
C-Reactive Protein, mg/L	**Mean (SD)**	NR		NR	
	> ULN#, n (%)	526 (22.0)	357 (18.9)	723 (37.2)	722 (37.1)
eGFR, mean mL/min/1.73 m^2 (SD)		19.72 (11.6)	20.04 (11.8)	NR	
HDL-C, mean mg/dL (SE)		45.45 (0.7)§	45.45 (0.7)§	43.04 (1.26)§	43.67 (1.27)§
LDL-C, mean mg/dL (SD)		98.97 (44.15)	95.53 (42.40)	93.25 (39.78)	93.02 (39.36)
Total Cholesterol, mean mg/dL (SE)		176.22 (1.40)§	172.73 (2.1)§	168.99 (1.26)§	169.62 (1.27) §

CKD: chronic kidney disease, DD: dialysis-dependent, DI: dialysis-independent, dL: deciliter, EPO: epoetin alfa, eGFR: estimated glomerular filtration rate, g: gram, HDL-C: high-density lipoprotein cholesterol, L: liter, LDL-C: low-density lipoprotein cholesterol, m^2: square meter, min: minute, mg: milligram, mL: milliliter, µg: microgram, N/A: not applicable, N: total number, n: number, ng: nanogram, NR: not reported, PBO: placebo, ROX: roxadustat, SD: standard deviation, SE: standard error ULN: upper of limit normal

*Assumption made based on study protocol.

†Converted from µg/dL to mg/L.

‡Ferritin ≥100 ng/mL and TSAT ≥20%.

§Data are digitized and should be interpreted with caution.

#Defined as 4.9 mg/L.

Evidence Table 33. Efficacy Outcomes

Trials			DI-CKD *(ALPS, ANDES, OLYMPUS)*[17,22,97,98]		DD-CKD *(HIMALAYAS, ROCKIES, SIERRAS)*[17,22,97,98]	
Arms			**ROX (N=2391)**	**PBO (N=1886)**	**ROX (N=1943)**	**EPO (N=1947)**
Change in Hb, g/dL	**Timepoint**		Average of Weeks 28 to 52			
	N		2931	1886	1612	1634
	Mean (SE)		1.85 (NR)	0.13 (NR)	1.22 (NR)	0.99 (NR)
	Between Group Difference	**LSM (95% CI), p-value**	NR, <0.001		NR, <0.001	
Hb Response	**Timepoint**		Week 24			
	N		2391	1886	NR	
	n (%)		1918 (80.2)	164 (8.7)		
	Between Group Difference	**Mean % (95% CI), p-value**	71.5 (69.4, 73.5), <0.001			
Change in eGFR in Patients with Baseline eGFR ≥15 mL/min/1.73 m²	**Timepoint**		Week 52			
	N		990	657	NR	
	Mean (SE)		-1.88 (0.27)*	-2.49 (0.32)*		
	Between Group Difference	**LSM (95% CI), p-value**	1.60 (NR), <0.0001			
Use of Rescue Therapy	**Timepoint**		Week 52			
	N		NR		NR	
	n (%)		213 (8.9)	587 (31.1)		
	Time to Event	**HR (95% CI), p-value**	0.19 (0.16, 0.23), <0.0001			
Use of Blood Transfusion	**Timepoint**		Week 52			
	N		NR		NR	
	n (%)		124 (5.2)	290 (15.4)	183 (9.5)	247 (12.8)
	Time to Event	**HR (95% CI), p-value**	0.26 (0.21, 0.32), <0.0001		0.82 (0.679, 0.997), 0.046	
Monthly IV Iron Use	**Timepoint**		Average of Weeks 28 to 52			
	n (%)		NR		NR	
	Mean mg (SD)				80.30 (NR)	108.20 (NR)

Trials			DI-CKD *(ALPS, ANDES, OLYMPUS)*[17,22,97,98]		DD-CKD *(HIMALAYAS, ROCKIES, SIERRAS)*[17,22,97,98]	
Arms			**ROX (N=2391)**	**PBO (N=1886)**	**ROX (N=1943)**	**EPO (N=1947)**
	Between Group Difference	**LSM (95% CI), p-value**			NR p<0.0001	
Change in Hepcidin, ng/mL	**Timepoint**		Week 24			
	N		1456	913	1326	1361
	Mean (SD)		-23.05 (86.03)	12.33 (87.77)	-60.35 (134.55)	-34.08 (137.37)
	Between Group Difference	**Mean (95% CI), p-value**	NR, <0.0001		NR, <0.0001	
Change in Transferrin, mg/L	**Timepoint**		Average of Weeks 12 to 28			
	N		2149	1604	1735	1817
	Mean (SD)		0.41 (0.58)[†]	-0.02 (0.42)[†]	0.37 (0.58)[†]	0.005 (0.55)[†]
	Between Group Difference	**Mean (95% CI), p-value**	NR		NR	
Change in TSAT, %	**Timepoint**		Average of Weeks 12 to 28			
	N		2148	1597	750	750
	Mean % (SD)		-1.15 (11.82)	0.38 (10.69)	-1.70 (13.70)	-2.70 (12.43)
	Between Group Difference	**Mean (95% CI), p-value**	NR		NR	
Change in Serum iron, µg/dL	**Timepoint**		Average of Weeks 12 to 28			
	N		2152	1604	1737	1819
	Mean (SD)		6.85 (30.58)	0.80 (27.37)	4.83 (34.30)	-5.70 (35.33)
	Between Group Difference	**Mean (95% CI), p-value**	NR		NR	
Change in Ferritin, ng/mL	**Timepoint**		Average of Weeks 12 to 28			
	N		2155	1604	1736	1819
	Mean (SD)		-76.14 (169.41)	-5.88 (149.84)	-142.02 (289.18)	-102.39 (321.83)
	Between Group Difference	**Mean (95% CI), p-value**	NR		NR	
Change in HDL-C, mg/dL	**Timepoint**		Average of Weeks 12 to 28			

Trials			DI-CKD *(ALPS, ANDES, OLYMPUS)*[17,22,97,98]		DD-CKD *(HIMALAYAS, ROCKIES, SIERRAS)*[17,22,97,98]	
Arms			**ROX (N=2391)**	**PBO (N=1886)**	**ROX (N=1943)**	**EPO (N=1947)**
	N		NR		NR	
	Mean (SE)		41.26 (1.4)*	45.45 (1.4)*	38.61 (0.63)*	43.04 (0.63)*
	Between Group Difference	**LSM (SE), p-value**	-4.14 (0.41), <0.0001		-4.15 (0.32), <0.0001	
Change in LDL-C, mg/dL	**Timepoint**		Average of Weeks 12 to 28			
	N		2368	1865	1929	1928
	Mean (SD)		81.83 (36.19)	97.55 (43.79)	76.67 (32.95)	91.81 (38.54)
	Between Group Difference	**LSM (95% CI), p-value**	-19.83 (-22.16, -17.51), <0.001		-15.80 (-17.54, -14.06), <0.0001	
Change in Total Cholesterol, mg/dL	**Timepoint**		Average of Weeks 12 to 28			
	N		NR		NR	
	Mean (SE)		151.75 (2.1)*	175.52 (2.1)*	144.94 (1.26)*	167.09 (1.9)*
	Between Group Difference	**LSM (SE), p-value**	-27.54 (1.51), <0.0001		-22.69 (1.12), <0.0001	
No data reported for the following outcomes: Use of ESA treatment, soluble transferrin receptor, total iron binding capacity						

95% CI: 95% confidence interval, CKD: chronic kidney disease, DD: dialysis-dependent, DI: dialysis-independent, dL: deciliter, EPO: epoetin alfa, eGFR: estimated glomerular filtration rate, g: gram, Hb: hemoglobin, HDL-C: high-density lipoprotein cholesterol, HR: hazard ratio, L: liter, LDL-C: low-density lipoprotein cholesterol, LSM: least squares mean, m^2: square meter, min: minute, mg: milligram, mL: milliliter, µg: microgram, N: total number, n: number, ng: nanogram, NR: not reported, PBO: placebo, ROX: roxadustat, SD: standard deviation, SE: standard error, SEM: standard error of means

*Data are digitized and should be interpreted with caution.

†Converted from µg/dL to mg/L.

Evidence Table 34. Efficacy Outcomes – Subgroups (DI-CKD)

Trials			DI-CKD *(ALPS, ANDES, OLYMPUS)*[17,22,53-55]							
Population			Iron Replete‡		Iron Deplete#		CRP >ULN†		CRP ≤ULN†	
Arm			ROX	PBO	ROX	PBO	ROX	PBO	ROX	PBO
Change in Hb, g/dL	Timepoint									
	N		1433	1127	956	755	526	357	1222	855
	LSM (SE)		1.94 (0.03)	0.13 (NR)	1.94 (0.03)	0.33 (NR)	Mean: 1.95 (SEM: 0.02*)	0.36 (SEM: 0.04*)	1.88 (SEM: 0.03*)	0.1 (SEM: 0.04*)
	Between Group Diff.	LSM (95% CI), p-value	1.81 (1.71, 1.90), <0.0001		1.61 (1.50, 1.72), <0.0001		1.67 (1.53, 1.82), <0.0001		1.74 (1.65, 1.82), <0.0001	
Use of Rescue Therapy	Timepoint		52 Weeks							
	N		NR	NR	NR	NR	NR		NR	
	n (%)		NR	NR	NR	NR				
	Incidence Rate Difference	Mean (95% CI), p-value	-24.3 (-27.43, -21.12), NR		-18.9 (-22.58, -15.29), NR					
Use of Blood Transfusion	Timepoint		52 Weeks							
	N		1420	1114	947	748	NR		NR	
	n (%)		82 (5.8)	189 (17)	41 (4.3)	98 (13.1)				
	Time to Event	HR (95% CI), p-value	0.25 (0.19, 0.33), <0.0001		0.26 (0.18, 0.38), <0.0001					
Use of IV Iron, no	Timepoint		52 Weeks							
	N		1420	1114	947	748	NR		NR	
	n (%)		33 (2.3)	47 (4.2)	29 (3.1)	65 (8.7)				
	Time to Event	HR (95% CI), p-value	0.44 (0.28, 0.70), 0.0004		0.3 (0.19, 0.47), <0.0001					
Change in TSAT, %	Timepoint									
	N		1111	770	735	511	NR		NR	
	Mean (SD)		-2.59 (NR)	-2.34 (NR)	4.88 (NR)	4.28 (NR)				
	Between Group Diff.	Mean (95% CI), p-value	NR		NR					
No data reported for the following outcomes: Hb response, eGFR, hepcidin, transferrin, transferrin saturation, serum iron, ferritin, HDL-C, LDL-C, total cholesterol										

95% CI: 95% Confidence interval, CKD: chronic kidney disease, DI: dialysis-independent, dL: deciliter, g: gram, eGFR: estimated glomerular filtration rate, Hb: hemoglobin, HDL-C: high-density lipoprotein cholesterol, HR: hazard ratio, L: liter, LDL-C: low-density lipoprotein cholesterol, LSM: least squares mean, mg: milligram, mL: milliliter, µg: microgram, N: total number, n: number, ng: nanogram, NR: not reported, PBO: placebo, ROX: roxadustat, SD: standard deviation, SE: standard error, SEM: standard error of the mean

*Data are digitized and should be interpreted with caution.

†Defined as 4.9 mg/L.

‡Ferritin ≥100 ng/mL and TSAT ≥20%.

#Ferritin <100 ng/mL and TSAT <20%.

Evidence Table 35. Efficacy Outcomes – Subgroups (DD- and ID-CKD)

Trials			DD-CKD *(HIMALAYAS, ROCKIES, SIERRAS)*[22,57]				ID-CKD *(HIMALAYAS, ROCKIES, SIERRAS)* [22,58,59]	
Population			CRP >ULN†		CRP ≤ULN†		ID-CKD	
Arms			ROX (N=723)	EPO (N=722)	ROX (N=889)	EPO (N=912)	ROX (N=760)	EPO (N=770)
Change in Hb, g/dL	Timepoint		Average of Weeks 28 to 52				Average of Weeks 28 to 52	
	N		723	722	889	912	760	770
	Mean (SD)		1.30 (NR)	0.90 (NR)	1.30 (NR)	1.10 (NR	2.12 (1.45)	1.91 (1.42)
	Between Group Difference	LSM (95% CI), p-value	NR, <0.0001		NR, p<0.0001		0.22 (0.05, 0.40), 0.013	
Use of Blood Transfusion	Timepoint		NR					
	N						760‡	770‡
	n (%)						46 (6.1)	52 (6.7)
	Time to Event	HR (95% CI), p-value					0.99 (0.66, 1.47), NR	
Monthly IV Iron Use, mg	Timepoint		NR				Average of Weeks 28 to 52	
	N						NR	NR
	n (%)						NR	NR
	Mean (SD)						53.57 (143.10)	70.22 (173.33)
	Between Group Difference	LSM (95% CI), p-value					-40.8 (-77.3, -4.3), <0.0001	
Change in HDL-C, mg/dL	Timepoint		NR				Average of Weeks 12 to 28	
	N						NR	NR
	Mean (SE)						37.97 (0.64)*	43.04 (0.63)*
	Between Group Difference	LSM (SE), p-value					-3.85 (0.807), <0.0001	
Change in LDL-C, mg/dL	Timepoint		NR				Average of Weeks 12 to 28	
	N						756	759
	Mean (SD)						−22.57 (29.94)	−4.79 (27.89)
	Between Group Difference	LSM (95% CI), p-value					-17.50 (-22.22, -12.78), <0.0001	
Change in Total Cholesterol, mg/dL	Timepoint		NR				Average of Weeks 12 to 28	
	N						NR	NR
	Mean (SE)						150.63 (1.9)*	175.32 (2.53)*
	Between Group Difference	LSM (SE), p-value					-23.31 (3.01), <0.0001	
Data for the following outcomes not reported: Hb response, rescue therapy, blood transfusion, hepcidin, transferrin, transferrin saturation, serum iron, ferritin								

95% CI: 95% Confidence interval, CKD: chronic kidney disease, CRP: c-reactive protein, DD: dialysis-dependent, DI: dialysis-independent, dL: deciliter, EPO: epoetin alfa, eGFR: estimated glomerular filtration rate, g: gram, Hb: hemoglobin, HDL-C: high-density lipoprotein cholesterol, HR: hazard ratio, IV: intravenous, L: liter, LDL-C: low-density lipoprotein cholesterol, LSM: least squares mean, m^2: square meter, min: minute, mg: milligram, mL: milliliter, µg: microgram, N: total number, n: number, ng: nanogram, NR: not reported, PBO: placebo, ROX: roxadustat, SD: standard deviation, SE: standard error, SEM: standard error of means, LN: upper limit of normal

*Data are digitized and should be interpreted with caution.

†Defined as 4.9 mg/L.

‡ITT population assumed given no other Ns were reported.

Evidence Table 36. Patient Reported Outcomes

Trials			DI-CKD *(ALPS, ANDES, OLYMPUS)*[48]		DD-CKD *(HIMALAYAS, ROCKIES, SIERRAS)*[48]	
Timepoint			12 weeks			
Arm			ROX	PBO	ROX	EPO
Change in SF-36 Physical Functioning, Points	**N**		2352	1851	NR	
	LSM (SE)		1.23 (0.21)*	0.7 (0.21)*		
	Between Group Difference	**LSM (95% CI), p-value**	0.53 (0.05, 1.01), 0.0311			
Change in SF-36 Vitality, Points	**N**		2351	1852	NR	
	LSM (SE)		2.58 (0.22)*	1.63 (0.21)*		
	Between Group Difference	**LSM (95% CI), p-value**	0.96 (0.44, 1.47) 0.0003			
Change in FACT-An Anemia, Points	**N**		2346	1854	NR	
	LSM (SE)		3.17 (0.26)*	2.08 (0.31)*		
	Between Group Difference	**LSM (95% CI), p-value**	1.10 (0.45, 1.74), 0.0008			
Change in FACT-An Total Score, Points	**N**		2345	1852	NR	
	LSM (SE)		4.86 (0.49)*	3.05 (0.58)*		
	Between Group Difference	**LSM (95% CI), p-value**	1.81 (0.54, 3.08), 0.0051			
Change in EQ-5D-5L VAS Score, Points	**N**		2350	1853	NR	
	LSM (SE)		2.93 (0.34)*	1.25 (0.43)*		
	Between Group Difference	**LSM (95% CI), p-value**	1.68 (0.76, 2.59), 0.0003			
PGIC Response	**N**		2368	1865	NR	
	n (%)		720 (30.4)	421 (22.6)		
	Between Group Difference	**OR (95% CI), p-value**	2.03 (1.74, 2.36), <0.0001			

95% CI: 95% Confidence interval, CKD: chronic kidney disease, DD: dialysis-dependent, DI: dialysis-independent, EPO: epoetin alfa, EQ-5D-5L: European Quality of Life Questionnaire-5 Dimensions-5 Levels, FACT-An: Functional Assessment of Cancer Therapy – Anemia, LS: least squares, N: total number, n: number, NR: not reported, OR: odds ratio, PBO: placebo, ROX: roxadustat, SE: standard error, SF-36: 36-Item Short Form Survey, VAS: visual analog scale

*SEs were digitized and should be interpreted with caution.

Evidence Table 37. Patient Reported Outcomes – Subgroups

Trials			DI-CKD *(ALPS, ANDES, OLYMPUS)*[48]								DD-CKD *(HIMALAYAS, ROCKIES, SIERRAS)*[48]			
Population			Iron Replete		Iron Deplete		CRP >ULN*		CRP ≤ULN*		CRP >ULN*		CRP ≤ULN*	
Timepoint			12 weeks											
Arm			ROX	PBO	ROX	PBO	ROX	PBO	ROX	PBO	ROX	EPO	ROX	EPO
Change in SF-36 Physical Functioning, Points	N		NR				520	351	1206	848	NR			
	Mean (SD)						0.96 (8.71)	0.26 (8.87)	1.22 (7.94)	0.85 (7.60)				
	Between Group Difference	LSM (95% CI), p-value					0.51 (-0.61, 1.64), 0.3711		0.66 (-0.00, 1.31), 0.051					
Change in SF-36 Vitality, Points	N		NR				519	351	1206	849	NR			
	Mean (SD)						3.23 (9.62)	2.45 (9.67)	2.67 (8.91)	1.91 (8.75)				
	Between Group Difference	LSM (95% CI), p-value					0.97 (-0.25, 2.18), 0.1191		1.05 (0.33, 1.78), 0.0043					
Other subscales not reported														

95% CI: 95% Confidence interval, CKD: chronic kidney disease, CRP: C-reactive protein, DD: dialysis-dependent, DI: dialysis-independent, diff.: difference, EPO: epoetin alfa, LSM: least square mean, N: total number, n: number, NR: not reported, PBO: placebo, ROX: roxadustat, SD: standard deviation, SF-36: 36-Item Short Form Survey, ULN: upper limit of normal

*Defined as 4.9 mg/L.

Evidence Table 38. CV Safety

Trials			DI-CKD *(ALPS, ANDES, OLYMPUS)*[17,22]		DD-CKD *(HIMALAYAS, ROCKIES, SIERRAS)*[17,22]	
Timepoint			During the Study Period		Week 52	
Arm			ROX (N=2391)	PBO (N=1886)	ROX (N=1940)	EPO (N=1940)
MACE*	n (%)		NR		NR	
	Time to Event	HR (95% CI), p-value	1.08 (0.94, 1.24), NR		0.96 (0.82, 1.13), NR	
MACE+†	n (%)		NR		NR	
	Time to Event	HR (95% CI), p-value	1.04 (0.91, 1.18),		0.86 (0.74, 0.98), 0.028	
Myocardial Infarction	n (%)		NR		103 (5.3)	109 (5.6)
	Time to Event	HR (95% CI), p-value			NR	
Stroke	n (%)		NR		45 (2.3)	50 (2.6)
	Time to Event	HR (95% CI), p-value			NR	
Unstable Angina Requiring Hospitalization	n (%)		NR		18 (0.9)	22 (1.1)
	Time to Event	HR (95% CI), p-value			NR	
Congestive Heart Failure Requiring Hospitalization	N		2386	1884	1940	1940
	n (%)		NR		120 (6.2)	166 (8.6)
	Time to Event	HR (95% CI), p-value	0.89 (0.72, 1.12), NR		0.73 (0.58, 0.94), 0.013	

95% CI: 95% confidence interval, CKD: chronic kidney disease, DD: dialysis-dependent, DI: dialysis-independent, diff.: difference, EPO: epoetin alfa, HR: hazard ratio, MACE: major adverse cardiovascular event, N: total number, n: number, NR: not reported, ns: not significant, PBO: placebo, ROX: roxadustat

*Defined as all-cause mortality (not cardiovascular mortality), myocardial infarction, or stroke.

†Defined as MACE or unstable angina requiring hospitalization or congestive heart failure requiring hospitalization.

Evidence Table 39. Cardiovascular Safety – Subgroup (ID-CKD)

Trials			DI-CKD *(ALPS, ANDES, OLYMPUS)*	DD-CKD *(HIMALAYAS, ROCKIES, SIERRAS)*	ID-CKD *(HIMALAYAS, ROCKIES, SIERRAS)*[58]	
Timepoint			NR	NR	On Treatment + 7 Days	
Arm					ROX (N=760)	EPO (N=776)
MACE*	Events (incidence/100 PEY)				74 (6.7)	97 (8.)2
	Time to Event	HR (95% CI), p-value			0.70 (0.51, 0.96), 0.029	
MACE+†	Events (incidence/100 PEY)				88 (8.0)	121 (10.2)
	Time to Event	HR (95% CI), p-value			0.66 (0.50, 0.89), 0.005	
All-cause Mortality	Events (incidence/100 PEY)				52 (4.7)	70 (5.8)
	Time to Event	HR (95% CI), p-value			0.76 (0.52, 1.11), 0.154	
MI	Events (incidence/100 PEY)				21 (1.9)	18 (1.5)
	Time to Event	HR (95% CI), p-value			1.17 (0.59, 2.32), NR	
Stroke	Events (incidence/100 PEY)				11 (1.0)	20 (1.7)
	Time to Event	HR (95% CI), p-value			0.41 (0.18, 0.94), 0.035	
Unstable Angina Requiring Hospitalization	Events (incidence/100 PEY)				6 (0.5)	6 (0.5)
	Time to Event	HR (95% CI), p-value			0.90 (0.26, 3.11), 0.87	
Congestive Heart Failure Requiring Hospitalization	Events (incidence/100 PEY)				25 (2.3)	28 (2.4)
	Time to Event	HR (95% CI), p-value			0.77 (0.42, 1.40), 0.39	

95% CI: 95% confidence interval, CKD: chronic kidney disease, DD: dialysis-dependent, DI: dialysis-independent, diff.: difference, EPO: epoetin alfa, HR: hazard ratio, ID: incidence-dialysis, MACE: major adverse cardiovascular event, N: total number, n: number, NR: not reported, ns: not significant, PEY: patient exposure years, ROX: roxadustat

*Defined as all-cause mortality (not cardiovascular mortality), myocardial infarction, or stroke.

†Defined as MACE or unstable angina requiring hospitalization or congestive heart failure requiring hospitalization.

Evidence Table 40. Safety

Trials			DI-CKD *(ALPS, ANDES, OLYMPUS)*[17,22,102]		DD-CKD *(HIMALAYAS, ROCKIES, SIERRAS)*[17,22,102]	
Arms			**ROX (N=2391)**	**PBO (N=1886)**	**ROX (N=1929)**	**EPO (N=1928)**
Timepoint			Treatment Period + 28 Days			
Any AE, n (%)			NR		NR	
Any TEAE, n (%)			2138 (89.4)	1611 (85.4)	NR	
Study Drug-Related AEs, n (%)			NR		NR	
Serious AEs, n (%)			NR		NR	
Serious TEAEs, n (%)			NR		NR	
D/C due to AEs, n (%)			NR		NR	
All-Cause Mortality	**n (%)**		NR	NR	207 (10.7)	232 (12.0)
	Time to Event	**HR (95% CI), p-value**	1.06 (0.91, 1.23)*, NR		0.96 (0.79, 1.17)†, NR	
Hospitalization, n (%)			NR		NR	
End Stage Renal Disease, n (%)			NR		NR	
Decline in eGFR, n (%)			NR		NR	
Pulmonary Embolism, n (%)			NR		NR	
Hypertensive Emergency, events/100 patient-exposure years†			1.1	1.1	2.2	2.5
Pulmonary Hypertension, n (%)			NR		NR	
Exacerbation of Hypertension‡§	**n (%)**		NR		NR	
	Time to Exacerbation of Hypertension	**HR (95% CI), p-value**	1.12 (0.95, 1.32), NR		1.06 (0.93, 1.21), NR	

95% CI: 95% confidence interval, AE: adverse event, CKD: chronic kidney disease, D/C: discontinuation, DD: dialysis-dependent, DI: dialysis-independent, eGFR: estimated glomerular filtration rate, EPO: epoetin alfa, HR: hazard ratio, N: total number, n: number, NR: not reported, ns: not significant, PBO: placebo, ROX: roxadustat, TEAE: treatment-emergent adverse event

*During the study period.

†In the first 52 weeks.

‡Time period not reported.

§Systolic blood pressure (SBP) ≥170 mmHg or diastolic blood pressure (DBP) ≥110 mmHg and an increase from baseline ≥20 mmHg (SBP) or ≥15 mmHg (DBP).

D4. Heterogeneity and Subgroups

We did not identify any RCTs that assessed the impact of roxadustat on subgroups of patients with cardiovascular disease or cancer. As seen in Evidence Table 1 and Evidence Table 17, these patients were excluded from the RCTs. RCTs that investigated the impact of roxadustat on subgroups of patients defined by iron and inflammation states, CKD G-stages III, IV, or V, or patients with incident DD-CKD are described below.

DI-CKD

Subgroups Defined by Iron and Inflammation States

DOLOMITES RCT (roxadustat vs. darbepoetin alfa): Data regarding subgroups based on iron or inflammation states for DOLOMITES are unavailable at the time of this report.

ALPS, ANDES, and OLYMPUS RCTs (roxadustat vs. placebo): We identified nine references for subgroup analyses of the key RCTs and pooled analysis.[17,19,22,48,52-56] The results demonstrated significant improvements with roxadustat compared to placebo (on use of rescue therapy, blood transfusion, IV iron supplementation, change in Hb, and change in TSAT) regardless of iron states (see Evidence Table 6, Evidence Table 7, Evidence Table 34, and Evidence Table 37). Further, the results showed significant improvements in change in Hb with roxadustat compared to placebo regardless of inflammation states, though the differences reported in HRQoL did not meet MCIDs (see Evidence Table 34 and Evidence Table 37). Qualitatively, there were no subgroup effects based on iron or inflammation states.

Subgroups Defined by Stages of CKD: G-Stages III, IV, and V

DOLOMITES RCT (roxadustat vs. darbepoetin alfa): Data regarding subgroups based on stages of CKD for DOLOMITES are unavailable at the time of this report.

ANDES RCT (roxadustat vs. placebo): We identified one reference for subgroup analyses of CKD G-stages III, IV, and V.[18] The results demonstrated significant improvements with roxadustat compared to placebo on change in Hb regardless of CKD G-stage (see Evidence Table 7). The treatment difference estimate was largest in CKD G-stage V followed by IV with non-overlapping confidence intervals between results from CKD G-stage III and V.

DD-CKD

Subgroups Defined by Iron and Inflammation States

We identified three references for subgroup analyses of HIMALAYAS, ROCKIES, SIERRAS, and a pooled analysis of these RCTs.[22,24,57] The results demonstrated that roxadustat resulted in

significant improvements compared to epoetin alfa (on change in Hb) regardless of iron and inflammation states (see Evidence Table 24 and Evidence Table 35). Qualitatively, there were no subgroup effects based on iron or inflammation states. However, comparable data for PYRENEES are unavailable at the time of this report.

Other RCTs demonstrated similar trends regardless of inflammation state, though statistical values were not reported.[44,103]

Incident Dialysis Subgroup

We identified two references for subgroup analyses of incident DD-CKD patients.[58,59] As described above, the HIMALAYAS RCT only included incident DD-CKD patients, while in the ROCKIES and the SIERRAS RCTs, 10% and 20% of the enrolled patients, respectively, were incident DD-CKD patients. A pooled analysis of HIMALAYAS and the incident DD-CKD subgroups of ROCKIES and SIERRAS showed the risk of MACE and MACE+ was significantly reduced with roxadustat compared to placebo; however, there was no significant difference in the risk of all-cause mortality (see Evidence Table 39). Because these endpoints were not available for the stable DD-CKD subgroups of ROCKIES and SIERRAS at the time of this report, we were unable to assess whether these results differ. However, as mentioned previously, in a pooled analysis of HIMALAYAS, ROCKIES, and SIERRAS, only the risk of MACE+ was significantly reduced with roxadustat compared to epoetin alfa.[17]

D5. Ongoing Studies

Table D12. Ongoing Studies

Trial	Study Design	Study Arms	Patient Population	Key Outcomes	Estimated Completion Date
Different Doses of Roxadustat Treatment for Anemia in Peritoneal Dialysis Patients NCT04454879 **Sponsors:** **Peking University First Hospital** **Beijing Haidian Hospital** **Beijing Hospital of Traditional Chinese Medicine**	Phase IV, randomized, open-label study Estimated N: 100 Location: China	Roxadustat (oral) Standard dosage (weight based) Lower dosage (weight based)	Inclusion Criteria: • CKD Stage V • Maintenance on PD for ≥3 months • Renal anemia, and Hb between 90g/L-120g/L • Stop taking erythropoietin for enough time or free of erythropoietin use Exclusion Criteria: • Hematologic malignancy or aplastic anemia • Blood loss or hemolysis • Currently taking roxadustat, or allergy or intolerance to roxadustat • Severe liver injury or active hepatitis • Cancer, receiving radiotherapy and chemotherapy within 6 months • Refractory hypertension	[Timeframe: 12 weeks] Primary Outcome(s): • The ratio of Hb achieving the target (115g/L) Secondary Outcome(s): • Variation ratio of Hb levels • The ratio of Hb over-shooting (> 130g/L)	March 2022
Post-marketing Surveillance of EVRENZO® Tablets (Roxadustat) in Dialysis-dependent Patients with Renal Anemia NCT04408820 **Sponsor:**	Prospective cohort study Estimated N: 1000 Location: Japan	Roxadustat (oral)	Inclusion Criteria: • Renal anemia patients on dialysis who are naïve to roxadustat Exclusion Criteria: • N/A	[Timeframe: Up to 104 Weeks] Primary Outcome(s): • CFB in Hb levels • Mean value of Hb levels over time • Achievement rate for target Hb level • Mean Hb levels at 4 weeks after switching to roxadustat • Proportion of participants with • Adverse drug reactions (ADRs)	November 2023

Trial	Study Design	Study Arms	Patient Population	Key Outcomes	Estimated Completion Date
Astellas Pharma Inc.				• Serious ADRs • Thromboembolism • Hypertension • Hepatic function disorder • Malignant tumors • Retinal hemorrhage • Myopathy events • ADR within 4 weeks after switching to roxadustat • ADR with high doses of roxadustat	
A Prospective Cohort Study of Roxadustat for Anemia in Patients With CKD **NCT04502537** **Sponsor: Shenzhen Second People's Hospital**	Prospective cohort study Estimated N: 200 Location: China	Roxadustat (oral) Erythropoietin (IV)	Inclusion Criteria: • ≥18 years of age • Hb level of <10 g/dL if patient received ESA treatment • Hb level of ≥7 and ≤ 12 g/dL if patient has received ESA treatment for ≥4 weeks • Expected survival time ≥1 year Exclusion Criteria: • History of severe, chronic, end-stage or uncontrolled autoimmune liver disease, Child Pugh score was grade C, or with active hepatitis • Anemia caused by any other disease other than CKD • Malignant tumor • RBC infusion during screening period	[Timeframe: Up to 52 weeks] Primary Outcome(s): • Mean value of Hb levels over time • Achievement rate for target Hb level Secondary Outcome(s): • Mean Hb levels at 4 and 8 weeks after using roxadustat • Dose of roxadustat used • CFB in Hb levels • Proportion of patients with different Hb levels • Proportion of patients with low response to ESA • Serum iron • AEs	September 2023
Study of Roxadustat Conversion in Subjects Receiving Stable ESA or as Initial Anemia	Phase III, open label, single group assignment trial	Roxadustat (oral)	Inclusion Criteria: ≥18 years of age • Receiving chronic dialysis for ESRD • Vascular access must be functioning native arteriovenous fistula or graft	[Timeframe: week 16 to 24] Primary Outcome(s): Proportion of subjects with mean Hb ≥10g/dL Mean Hb CFB	August 2021

Trial	Study Design	Study Arms	Patient Population	Key Outcomes	Estimated Completion Date
Treatment in Hemodialysis Patients NCT04484857 **Sponsor: FibroGen**	Estimated N: 300 Location: US		with adequate flow, or permanent tunneled catheter • Subjects converting from ESA: between 9.0-12.0 g/dL • Subjects initiating anemia treatment: <10.0 g/dL • Ferritin ≥50 ng/mL, TSAT ≥10% • ALT and AST ≤3 x ULN, and total bilirubin ≤1.5 x ULN • Weight 45-160 kg Exclusion Criteria: • RBC transfusion within 4 weeks • History of myelodysplastic syndrome, multiple myeloma, or malignancies • Hereditary hematologic disease or other known causes for anemia other than CKD • Active or chronic GI bleeding • Treated with iron-chelating agents within 4 weeks • NYHA Class III or IV CHF • History of MI, acute coronary syndrome, stroke, seizure • Uncontrolled hypertension • Diagnosis or suspicion of renal cell carcinoma		
Evaluate the Efficacy and Safety of Roxadustat for the Treatment of Anemia and Risks of Cardiovascular and Cerebrovascular	Phase IV, randomized, open label trial Estimated N: 400 Location: China	Roxadustat (oral) Epoetin alfa (IV)	[Timeframe: 52 weeks] Inclusion Criteria: • ≥18 years of age • Weight: 45-100 kg • Patients with CKD ESRD received HD treatment ≤4 weeks • No iron, folate, vitamin B12 deficiencies	Primary Outcome(s): • Mean Hb CFB to average levels from week 28-52 • Proportion of subjects who achieve a Hb response at 24 weeks • The incidence of CV and cerebrovascular events	October 2023

Trial	Study Design	Study Arms	Patient Population	Key Outcomes	Estimated Completion Date
Events in ESRD Newly Initiated Dialysis Patients **NCT04134026** **Sponsor:** **Second Xiangya Hospital of Central South University**			• No abnormal liver tests • Hb level <10.0 g/dL Exclusion Criteria: • Clinically significant infection or active potential infection • Active hepatitis or any of following abnormalities: ALT ≥2x ULN, AST ≥2x ULN, direct bilirubin ≥2x ULN • Patients with severe CVD have had MI, coronary artery bypass, or PCI operation within 3 months • Severe cerebrovascular diseases within 3 months • Active GI bleeding occurred within 3 months • Poorly controlled hypertension • Previous or current malignancies • Causes of anemia other than CKD • Known autoimmune diseases • Any previous functional organ transplant or scheduled organ transplant or no kidney • Serum albumin <25 g/L • Treatment with androgen, deferoxamine, deferrone, or deferestron within 8 weeks • RBC within 4 weeks	Secondary Outcome(s): • All-cause mortality • Proportion of subjects with increased hypertension [Timeframe: 27 weeks] • Mean BP CFB to average levels from week 28-52 • Change of left ventricular structure; change of systolic function; change of diastolic function at 12, 36, and 52 weeks • Serum lipid parameters [Timeframe: 25-27 Weeks] • Mean change level of CRP [Timeframe: 25-27 Weeks]	
Evaluate the Efficacy and Safety of Multiple Roxadustat Dosing Regimens for the Treatment of Anemia in Dialysis	Phase IV, randomized, open label trial Estimated N: 306	Part 1: Roxadustat low dose (oral) standard weight-based dose (oral)	Inclusion Criteria: • 18-75 years of age • CKD with ESRD on either HD or PD Exclusion Criteria: • HIV, hepatitis B surface antigen, or anti-hepatitis C virus antibody • CV risks	Primary Outcome(s): Part 1 (Weeks 1-20): • ESA-naïve: proportion of subjects who achieve Hb ≥11.0 g/dL in the first 20 weeks • ESA-treated: proportion of subjects who achieve mean Hb	

Trial	Study Design	Study Arms	Patient Population	Key Outcomes	Estimated Completion Date
Subjects with Chronic Kidney Disease **NCT04059913** **Sponsor: FibroGen**	Location: China	Part 2: Roxadustat Subjects will receive roxadustat at different dose frequencies	• History of malignancy, myelodysplastic syndrome, and multiple myeloma • Disease conditions that could impact RBC production • Recent blood loss	≥10.0 g/dL averaged over week 17 visit to week 21 Part 2 (Weeks 33-37) • Mean Hb averaged at weeks 33-37 visits Secondary Outcome(s): • Mean change in Hb level from baseline to average over weeks 17-21 • ESA-naïve: proportion of subjects with mean Hb (averaged week 17-21 visits) ≥10 g/dL • Proportion of subjects with mean Hb (averaged weeks 33-37 visits) ≥10 g/dL	

ALT: alanine transferase, AST: aspartate transferase, CKD: chronic kidney disease, CVD: cardiovascular disease, dL: deciliter, ESA: erythropoiesis-stimulating agent, ESRD: end-stage renal disease, g: gram, Hb: hemoglobin, HIV: human immunodeficiency virus, IV: intravenous, kg: kilogram, L: liter, MI: myocardial infarction, N: total number, N/A: not available, NYHA: New York Heart Association, PCI: Percutaneous Coronary Intervention, PD: peritoneal dialysis, RBC: red blood-cell, ULN: upper-limit of normal

Source: www.ClinicalTrials.gov (NOTE: studies listed on-site include both clinical trials and observational studies).

D6. Previous Systematic Reviews and Technology Assessments

We identified one ongoing health technology assessment (HTA) conducted by NICE and four previously conducted systematic reviews of roxadustat. These reviews are summarized below. It should be noted that none of the previous systematic reviews we identified include the key trials required for FDA review.

HTAs

NICE

Roxadustat for Treating Anaemia in People with Chronic Kidney Disease [ID1483]

NICE is currently conducting an appraisal of the clinical and cost effectiveness of roxadustat for the treatment of anemia associated with CKD. The expected publication date is to be confirmed.

Previous Systematic Reviews

Jia L, Dong X, Yang J, Jia R, Zhang H. Effectiveness of hypoxia-inducible factor prolyl hydroxylase inhibitor roxadustat on renal anemia in non-dialysis-dependent chronic kidney disease: a systematic review and meta-analysis. Ann Transl Med. 2019 Dec;7(23):720. doi: 10.21037/atm.2019.12.18. PMID: 32042736; PMCID: PMC6989965.

The authors conducted a systematic literature review and meta-analysis that included three Phase II RCTs evaluating roxadustat for the treatment of renal anemia in DI-CKD patients. Efficacy was evaluated based on changes in Hb levels from baseline and Hb response. Safety was evaluated based on the occurrence of AEs and serious AEs. Roxadustat was found to significantly increase Hb when compared to placebo. While roxadustat was generally found to be safe, the authors stated that significant uncertainties about the safety profile of roxadustat compared to placebo remain. The authors judged the clinical evidence to be of low and very low quality and found that the risk of bias was high because pharmaceutical companies sponsored all RCTs that were included in the NMA. The authors concluded that further independent research was needed to provide independent, high-quality evidence of the efficacy and safety of roxadustat.

Liu J, Zhang A, Hayden JC, Bhagavathula AS, Alshehhi F, Rinaldi G, Kontogiannis V, Rahmani J. Roxadustat (FG-4592) treatment for anemia in dialysis-dependent (DD) and not dialysis-dependent (NDD) chronic kidney disease patients: A systematic review and meta-analysis. Pharmacol Res. 2020 May;155:104747. doi: 10.1016/j.phrs.2020.104747. Epub 2020 Mar 17. PMID: 32171893.

This systematic review and meta-analysis were performed to evaluate the comparative efficacy and safety of roxadustat versus placebo and epoetin alfa for the treatment of anemia in patients with CKD. The meta-analysis included six RCTs (two Phase III and four Phase II trials), assessing roxadustat treatment in DI-CKD patients and patients receiving dialysis treatment (DD-CKD). It was found that in patients who were not on dialysis, roxadustat significantly increased Hb levels when compared to placebo. Similar results were found in the DD-CKD population, where roxadustat was shown to significantly increase Hb levels when compared to epoetin alfa. This meta-analysis found the safety profile of roxadustat and placebo to be comparable with regards to the occurrence of TEAEs in the DI-CKD population. However, in the DD-CKD population, roxadustat was found to significantly increase the risk of TEAEs when compared to epoetin alfa. The authors concluded that roxadustat is efficacious in increasing Hb levels in both DI- and DD-CKD patients. They also noted that the studies included in this meta-analysis were not powered to detect differences in safety or long-term clinical outcomes and that additional studies are needed to fill this gap.

Zheng Q, Yang H, Fu X, Huang Y, Wei R, Wang Y, Liu YN, Liu WJ. The efficacy and safety of roxadustat for anemia in patients with chronic kidney disease: a meta-analysis. Nephrol Dial Transplant. 2020 Oct 14:gfaa110. doi: 10.1093/ndt/gfaa110. Epub ahead of print. PMID: 33051677.

This systematic review and meta-analysis included six RCTs (two Phase III and four Phase II trials) evaluating the efficacy and safety of roxadustat for the treatment of renal anemia versus placebo in DI-CKD patients and versus epoetin alfa in DD-CKD patients. Roxadustat was found to lead to significantly higher Hb levels when compared to both placebo and epoetin alfa. The safety profile for roxadustat was found to be comparable to placebo in the DI-CKD patient population. When compared to epoetin alfa, however, DD-CKD patients treated with roxadustat experienced significantly more AEs. The incidence of serious AEs did not significantly differ with roxadustat compared to placebo and epoetin alfa. The authors noted that the quality of the clinical evidence was of low or very low quality. Nonetheless, the authors concluded that evidence suggests roxadustat is safe and efficacious in the short-term treatment of anemia in patients with CKD.

Zheng Q, Yang H, Sun L, Wei R, Fu X, Wang Y, Huang Y, Liu YN, Liu WJ. Efficacy and safety of HIF prolyl-hydroxylase inhibitor vs epoetin and darbepoetin for anemia in chronic kidney disease patients not undergoing dialysis: A network meta-analysis. Pharmacol Res. 2020 Sep;159:105020. doi: 10.1016/j.phrs.2020.105020. Epub 2020 Jun 16. PMID: 32561478.

This systematic review and NMA sought to compare HIF-PHIs versus ESAs for the treatment of anemia in DI-CKD patients. A total of 19 RCTs evaluating eight different anti-anemia treatment agents, including six HIF-PHIs (roxadustat, daprodustat, molidustat, enarodustat, desidustat, and vadadustat) and two ESAs (epoetin alfa and darbepoetin alfa) were included in this analysis. Efficacy was evaluated based on Hb level elevation and safety was assessed based on all-cause mortality. Roxadustat was found to lead to significantly greater change in Hb levels when compared to placebo, but not when compared to the two ESAs. All-cause mortality rates for DI-CKD patients treated with roxadustat, epoetin alfa, and darbepoetin alfa were comparable to those observed in those who received placebo. The authors concluded that while HIF-PHIs, such as roxadustat, are efficacious and well-tolerated, further studies are needed to evaluate their efficacy and safety profiles.

E. Long-Term Cost-Effectiveness: Supplemental Information

E1. Detailed Methods

Table E1. Impact Inventory

Sector	Type of Impact (Add Additional Domains, as Relevant)	Included in This Analysis from […] Perspective?		Notes on Sources (if Quantified), Likely Magnitude & Impact (if Not)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health Outcomes	Longevity effects	X	X	
	Health-related quality of life effects	X	X	
	Adverse events	X	X	
Medical Costs	Paid by third-party payers	X	X	
	Paid by patients out-of-pocket	☐	☐	
	Future related medical costs	X	X	
	Future unrelated medical costs	☐	☐	
Informal Health Care Sector				
Health-Related Costs	Patient time costs	NA	X	
	Unpaid caregiver-time costs	NA	X	
	Transportation costs	NA	☐	
Non-Health Care Sector				
Productivity	Labor market earnings lost	NA	X	
	Cost of unpaid lost productivity due to illness	NA	X	
	Cost of uncompensated household production	NA	X	
Consumption	Future consumption unrelated to health	NA	☐	
Social Services	Cost of social services as part of intervention	NA	☐	
Legal/Criminal Justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	☐	
Education	Impact of intervention on educational achievement of population	NA	☐	
Housing	Cost of home improvements, remediation	NA	☐	
Environment	Production of toxic waste pollution by intervention	NA	☐	
Other	Other impacts (if relevant)	NA	☐	

NA: not applicable

Adapted from Sanders et al.[104]

Target Population

Two target populations were considered: those with DI-CKD (CKD stages IIIb, IV, and V) and DD-CKD.

The DI-CKD population entered the model as CKD stage IIIb (60.6%), stage IV (23.6%), and stage V (15.8%), based on an analysis of commercial claims data for DI-CKD patients with anemia.[105] The baseline Hb for each population and for incident DD-CKD was presented in Table E2. Although anemia tends to worsen as CKD progresses, our DD-CKD cohort entered the model with a higher baseline Hb than the DI-CKD cohort, which was likely due to use of ESAs in the DD-CKD population prior to study enrollment.

Table E2. Baseline Population Characteristics

CKD Stage	Baseline Hb (g/dL)	Source
DI-CKD Stage IIIb	9.55	[21]
DI-CKD Stage IV	9.55	[17]
DI-CKD Stage V	9.55	[17]
DD-CKD	9.7	[17]

CKD: chronic kidney disease, DD: dialysis-dependent, DI: dialysis-independent, ESA: erythropoiesis stimulating agent, g/dL: grams per deciliter, Hb: hemoglobin

We considered subpopulations such as those newly on dialysis (incident dialysis) versus established, hyporesponsive to ESAs versus non-hyporesponsive, by iron repletion status, and those with co-morbid cancer or cardiovascular disease. The decision to separately evaluate subgroups is based on a complete review of the available data to determine if there is true subgroup effect. To date, only information pertaining to the incident-dialysis subpopulation is available to us. The observation that a larger reduction in MACE was observed in the incident-dialysis population compared with the overall DD-CKD population means conversely that a smaller reduction in MACE must be observed in the stable dialysis population. For this reason, we did not present results in the incident dialysis subpopulation without presenting a balanced interpretation of the results in the stable subpopulation. For the subpopulations of ESA-hyporesponsiveness, iron repletion status, or comorbid cancer or cardiovascular disease, limited data were available to inform stratification by subpopulation and/or the relative impact of the data available to us did not meaningfully change the results of the cost-effectiveness analysis.

Treatment Strategies

The intervention of interest is roxadustat (AstraZeneca).

In both populations, we intend to compare roxadustat to ESAs. The efficacy of ESAs was represented by the comparators within the roxadustat trial, with the assumption of equivalent efficacy across ESAs.

- Darbepoetin alfa (Aranesp, Amgen)
- Epoetin alfa (Epogen, Amgen; Procrit, Janssen)
- Epoetin alfa-epbx (Retacrit, Pfizer)
- Methoxy polyethylene glycol-epoetin beta (Mircera, Roche)

Cost of ESAs were represented by a market basket of ESAs. As data to inform a market basket for each population separately was not available to us, a consistent market basket was applied across the DI-CKD and DD-CKD populations consisting of darbepoetin alpha (28%), epoetin alpha (Epogen) (28%), epoetin alpha (Procrit) 15%, epoetin alpha-epbx (9%), and epoetin beta (20%).

E2. Model Inputs and Assumptions

Model Inputs

Transition Probabilities

The underlying transitions between CKD stages and death were based on prior published models of CKD, data from the US Renal Data System (USDRS) Annual Report, or for death in DD-CKD, the pooled roxadustat Phase III trials. The annual probability of death from the post-transplant health state was estimated based on a weighted averaged five-year survival of 84.7% from deceased donor recipients and 91.9% among living donor recipients, with 28% of patients receiving a kidney from a living donor.[106]

Table E3. Annual Transition Probabilities

	Ending State					
Initial State	**DI-CKD Stage IIIb**	**DI-CKD Stage IV**	**DI-CKD Stage V**	**DD-CKD**	**Transplant**	**Death†**
DI-CKD Stage IIIb	0.822*	0.137[107]	--	--	--	0.041[108]
DI-CKD Stage IV	--	0.839*	0.081[107]	--	--	0.080[108]
DI-CKD Stage V	--	--	0.257*	0.626[107]	0.009[107]	0.108[107]
DD-CKD	--	--	--	0.811*	0.035[106]	0.154†
Transplant	--	--	--	0.046[107]	0.926*	0.028[106, 107]

CKD: chronic kidney disease, DD: dialysis-dependent, DI: dialysis-independent

*Calculated by subtracting probabilities of all other transitions from 1.

†Based on the pooled analysis of the ESA arms of HIMALAYAS, SIERRAS, ROCKIES, and PYRENEES.

"--" represents no probability of transitioning to that state.

Clinical Inputs

Clinical Probabilities/Response to Treatment

Treatment effectiveness was estimated using the mean CFB in Hb level for roxadustat and ESAs from the roxadustat Phase III trials (Table E4). We estimated the treatment benefit of roxadustat over ESAs in the DD-CKD population based on a meta-analysis all four Phase III trials of HIMALAYAS, ROCKIES, PYRENEES, and SIERRAS. We also considered the proportion of patients who achieve Hb ≥10 g/dL.

Table E4. Treatment-Related Efficacy

Mean CFB in Hb	Roxadustat	ESA	Absolute Difference	Source
DI-CKD	1.85 g/dL	1.84 g/dL	0.015 (-0.13, 0.16)	[21]
DD-CKD	Based on meta-analysis	Based on meta-analysis	0.23 (-0.04, 0.50)	ICER meta-analysis
Hb Level, DI-CKD				
<10 g/dL	18%	18%*	None*	[21]
≥10 g/dL	82%	82%	None*	
Hb Level, DD-CKD				
<10 g/dL	33.9%	41.4%	-7.5%	[109]
≥10 g/dL	66.1%	58.6%	+7.5%	

CFB: change from baseline, CKD: chronic kidney disease, DD: dialysis-dependent, DI: dialysis-dependent, ESA: erythropoiesis stimulating agent, g/dL: grams per deciliter, Hb: hemoglobin, ICER: Institute for Clinical and Economic Review

*Assumed equal to roxadustat based on findings of a Phase III head-to-head, non-inferiority study.

Discontinuation

Patients continued treatment with roxadustat or ESAs with no discontinuation of treatment except for those in the post-transplant state. For the DI-CKD population all patients were assumed to switch to ESAs upon progression to DD-CKD in the base case.

Mortality

Patients with CKD are known to have increased risk of mortality, with increasing risk as the disease progresses. Overall mortality for CKD by health state was captured using published transition probabilities (see Table E3). Although not powered to detect a statistically significant difference, the Phase III trials of roxadustat showed a numeric reduction in mortality among patients treated with roxadustat compared with ESAs with a high degree of uncertainty. We considered a scenario where a potential reduction in all-cause mortality was considered based on point estimates, with 95% confidence intervals for those point estimates varied in one-way and probabilistic sensitivity analyses. Treatment-related impact on mortality were applied based on the relative reduction in risk of all-cause mortality from DOLOMITES in the DI-CKD population (0.83 [95% CI 0.50, 1.38]) *(scenario analysis only)*.[21] For the scenario which considered MACE+ events in the DI-CKD

population, a relative increase in mortality for DI-CKD patients after experiencing a MACE+ event was applied based on observational real-world data (HR 4.15 [95% CI 3.30, 5.23]).[110] For the DD-CKD population a relative reduction in risk of mortality for roxadustat compared with ESAs derived from a meta-analysis of all four Phase III trials of HIMALAYAS, ROCKIES, PYRENEES, and SIERRAS (RR 0.89 [95% CI 0.75, 1.06]).

Economic Inputs

Drug Utilization

For roxadustat and ESAs, dose adjustments are made to achieve and maintain Hb levels within a target range. For the DI-CKD population, average utilization was based on use of pre-filled syringes at a representative dose for each ESA. For DD-CKD, utilization was based on average units per cycle for epoetin alpha.[111] Epoetin alpha units per cycle were converted to darbepoetin alpha units per cycle based on a published conversion table.[72] Average utilization of epoetin beta was based on the median dose administered in a trial of DD-CKD patients.[112]

Table E5. Treatment Regimen Dosage and Utilization

	Darbepoetin Alfa	Epoetin Alfa	Methoxy Polyethylene Glycol-Epoetin Beta
Brand Name	Aranesp	Epogen, Procrit, Retacrit	Mircera
Manufacturer	Amgen	Amgen, Janssen	Roche
Route of Administration	IV or SC	IV or SC	SSC
Labeled Dosing in DI-CKD	Starting dose: 0.45 mcg/kg every 4 weeks	Starting dose: 50 to 100 units/kg 3 times weekly	Starting dose: 0.6 mcg/kg every 2 weeks Maintenance dose: 2x the starting dose every month
Labeled Dosing in DD-CKD	Starting dose: 0.45 mcg/kg every week or 0.75 mcg/kg every 2 weeks	Starting dose: 50 to 100 units/kg 3 times weekly	Starting dose: 0.6 mcg/kg every 2 weeks Maintenance dose: 1.2 mg per month
DI-CKD Utilization Assumption	One 40 mcg prefilled syringe administered SC per cycle	One 10,000-unit prefilled syringe administered SC 12 times per cycle	One 100 mcg/0.3 ml syringe administered SC per cycle
DD-CKD Utilization Assumption	160 mcg per cycle†	52,682 units per cycle*	120 mcg per cycle‡

CKD: chronic kidney disease, DD: dialysis-dependent, DI: dialysis-independent, IV: intravenous, kg: kilogram, mcg: microgram, SC: subcutaneous

*Based on weighted average of ESA non-responsive and hyporesponsive groups.[111]

†Based on converting epoetin alpha dose to darbepoetin dose.[72]

‡In the RUBRA (targeting sustained Hb in dialysis with IV and SC CERA. Administration) study, the median dose was 60 mcg once every two weeks during the evaluation period.[112]

Drug Acquisition Costs

Commercial Perspective

Roxadustat is not yet approved by the FDA and the drug cost is not yet available. At the time of the report, we had heard that analysts predict roxadustat to be priced at approximately $13,000 per year with a 50% discount. For ESAs in the base case from the commercial perspective, we used wholesale acquisition cost (WAC, October 2020 pricing) for subcutaneously-administered products in the DI-CKD population. Combining the net annual drug cost in Table E6 with the market share in Table E6 yields an average annual cost of $7,943 per year for ESAs in the DI-CKD population. For IV-administered products in the DD-CKD population we assumed ASP plus 9.5% to represent a commercial payer cost, yielding an average cost of $6,934 per year.

Medicare Perspective

For the Medicare perspective for the DD-CKD population, no costs for ESAs are itemized as these are reimbursed as part of a bundled payment. For roxadustat, we assumed incremental cost outside of the bundled payment equal to that of the commercial perspective ($6,500 per year) for three years, after which the roxadustat would be entered into the bundled payment.

Table E6. DI-CKD Drug Cost Inputs

Interventions	Administration	Unit	WAC per Unit/Dose*	Net Price per Units	Annual Drug Cost
Roxadustat	Oral	--	--	--	$6,500
Darbepoetin Alpha	SC	40 mcg syringe	$309.60	$134.06	$1,747
Epoetin Alpha (Epogen)	SC	10,000-unit syringe	$165.80	$81.41	$12,732
Epoetin Alpha (Procrit)	SC	10,000-unit syringe	$267.25	$108.77	$17,012
Epoetin Alpha-epbx	SC	10,000-unit syringe	$110.30	$71.25	$11,144
Epoetin Beta	SC	120 mcg syringe	$288.48	$128.09	$1,669

SC: subcutaneous, WAC: wholesale acquisition cost

*WAC as of October 20, 2020.

Table E7. DD-CKD ESA Drug Costs

Interventions	Administration	Unit	ASP per Unit/Dose*	ASP + 9.5%	Annual Drug Cost
Roxadustat	Oral	--	--	--	$6,500
Darbepoetin Alpha	IV	mcg	$3.506	$3.839	$8,005
Epoetin Alpha	IV	1,000 units	$8.593	$9.410	$6,461
Epoetin Alpha-epbx	IV	1,000 units	$8.125	$8.896‡	$6,108
Epoetin Beta	IV	mcg	$1.45	$1.595	$2,495

ASP: Average Sales Price, IV: intravenous

*ASP as of October 2020.

‡Calculated as ASP plus 9.5% of the originator product ASP.

Administration and Monitoring Costs

In the base case, it is assumed that DI-CKD patients will use self-administered formulations of subcutaneously-administered ESAs, resulting in no direct cost for administration. In the DD-CKD population, it is assumed that ESAs will be administered as part of regular dialysis sessions with no incremental cost of administration.

Direct Cost by CKD Stage

Direct cost of CKD by stage and transplant status were included in the model based on annual mean per-patient estimates from the USDRS 2018 and 2019 Annual Reports.[10,27] A one-time cost of undergoing transplant were based on CMS diagnosis-related group (DRG) amount (MS-DRG 652).[26] In the post-transplant state, some patients experienced graft failure as an adverse outcome of transplant, which was associated with significant cost. For the purposes of our model, those with graft failure were represented by the transition back to DD-CKD and incurred the cost of DD-CKD.

E8. Direct Cost of CKD

Cost Type	Cost	Source
Annual Cost of DI-CKD Stage IIIb	$22,000	[106]
Annual Cost of DI-CKD Stage IV and V	$33,000	[106]
Annual Cost of DD-CKD	$89,953	[113]
Transplant Event	$19,636	DRG 652*[114]
Annual Cost Post-Transplant, Functioning Graft	$26,988	[113]

CKD: chronic kidney disease, DD: dialysis-dependent, DI: dialysis-independent, DRG: diagnosis-related group, UPDRS: United States Renal Data System

*Sum of labor ($3,962.17) and non-labor ($1,838.96) national adjusted operating standardized amounts for wage index >1 and meaningful electronic health record user then multiplied by DRG weight of 3.3849.

Additionally, the cost of dialysis bundled payment will be considered under the Medicare perspective. For all patients with DD-CKD, a cost of $239.33 per encounter and 12 encounters per cycle will be applied based on rates from the CMS ESRD Prospective Payment System (PPS).[115]

Direct Cost of Anemia Management

In addition to drug cost, anemia management included red blood cell transfusions and IV iron supplementation. The utilization of these were taken directly from the roxadustat Phase III trials (Table E9, Table E10). Where information was unavailable separately for each population (DI-CKD and DD-CKD), we used the best available data applied to both populations.

From the commercial perspective, the cost of a red blood cell transfusion was informed by the Current Procedural Terminology (CPT) code for reimbursement for blood transfusion services (CPT 36430, $35.73), assuming one unit of blood per transfusion at a cost of $550.46 per unit.[116,117] This cost was based on a mean amount charged to the patient ($343.63 ± $135) in 2007 dollars, inflated to 2020 USD using the Personal Health Care Expenditure deflator up to 2017 and then the personal consumption expenditure price index to update to 2020. From the Medicare perspective, red blood cell transfusions are included in the bundle and have no incremental cost.

Table E9. RBC Transfusions over 52 Weeks

	ESA (95% CI)	HR for Roxadustat vs. ESAs (95% CI)	Source
DI-CKD	5.2%*	N/A*	[17,67]
DD-CKD	12.8% (11.3%, 14.3%)	0.82 (0.679, 0.997)	[17]

CI: confidence interval, CKD: chronic kidney disease, DD: dialysis-dependent, DI: dialysis-independent; ESA: erythropoiesis-stimulating agent, HR: hazard ratio, RBC: red blood cell

*Assumed equal to roxadustat based on findings of a Phase III head-to-head, non-inferiority study.

The cost of IV iron included both the cost of the drug and physician administration. From the commercial perspective, IV iron drug cost was based on ASP of ferumoxytol ($0.983 per unit) plus 9.5% and direct cost of administration was $72.18 (CPT 96365 National Payment Amount).[116,118] Iron dose administered per iron infusion was based on the recommended labeled dose of Feraheme® of an initial 510 mg dose followed by a second 510 mg dose three to eight days later.[119] No information was identified to inform the number of infusions for ESAs or roxadustat in the Phase III trials. For the draft model, one administration per cycle was assumed for both treatments. From the Medicare perspective, IV iron infusions are included in the bundle and have no incremental cost.

Table E10. IV Iron

	Roxadustat	ESA	HR (95% CI)	Source
DI-CKD	Calculated based on HR	21.2 infusions per 100 person-years	0.45 (0.26, 0.78)	[21]
DD-CKD	Calculated based on LSM difference	44.0 ± 88.6 mg per month	LSM difference: -31.9 mg (95% CI -41.4, -22.4)	[120]

CI: confidence interval, CKD: chronic kidney disease, DD: dialysis-dependent, DI: dialysis-independent; ESA: erythropoiesis stimulating agent, HR: hazard ratio, IV: intravenous, LSM: least squared mean, mg: milligram

Direct Cost of MACE+

Cost of MACE+ events included cost of the first cycle when the acute event occurred and cost of care for subsequent cycles attributable to higher health care resource utilization following MACE+ events. The cost of post-MI and post-stroke cycles was based on published three-year cumulative cost estimates, calculated as the total 36-month cost minus the first month divided by 35 months to arrive at a monthly long-term cost and then inflated to 2020 values.[29] Hospitalization for congestive heart failure and hospitalization for unstable angina were considered acute worsening events in patients with existing congestive heart failure and angina, respectively, and incurred costs only in the cycle when the event occurred.

Table E11. Cost of MACE+ Events

Parameter	Value*	Source
Death	$24,669	[121]
MI Event	$54,785	[121]
Unstable Angina Event	$27,713	[121]
Hospitalization for CHF	$7,807	DRG 291†[114]
Stroke Event	$16,980	Ischemic stroke[121]
Post-MI Cycles	$1,790	[121]
Post-Stroke Cycles	$430	[121]

CHF: congestive heart failure, CI: confidence interval, DRG: diagnosis-related group, MI: myocardial infarction
*Original 2007 values inflated to 2020 USD using the Personal Health Care Expenditure deflator up to 2017 and then the personal consumption expenditure price index to update to 2020.
†Sum of labor ($3,962.17) and non-labor ($1,838.96) national adjusted operating standardized amounts for wage index >1 and meaningful electronic health record user then multiplied by DRG weight of 1.3458.

Utility Tolls for MACE+

Table E12. Utility Tolls for MACE+ Events

Parameter	Value (95% CI)	Source
Unstable Angina Event (Applied to Cycle)	-0.0412	[122]
Hospitalization for CHF (Applied to Cycle)	-0.089 (-0.132, -0.047)	[123]
Acute Stroke Event (Applied to Cycle)	-0.204 (-0.272, -0.136)	[123]
Acute MI Event (Applied to Cycle)	-0.042 (-0.074, -0.010)	[123]
Post-Stroke Cycles	-0.101 (-0.117, -0.086)	[123]
Post-MI Cycles	-0.011 (-0.022, 0.001)	[123]

CHF: congestive heart failure, CI: confidence interval, MI: myocardial infarction

Indirect Costs

A modified societal perspective including indirect costs of presenteeism and absenteeism were included as a scenario analysis. Work Productivity and Activity Impairment Questionnaire (WPAI) estimates from a US patient survey were combined with USBLS average working hours per week (38.6) and average hourly wage ($29.47) to produce an indirect cost for each health state.[124,125]

Table E13. Overall Work Impairment (% of Time Impaired)

	Hb <10 % (SD)	Hb 10-12 % (SD)	Source
DI-CKD	37.4 (27.0)	28.9 (24.6)	[126]
DD-CKD	42.7 (29.3)	39.8 (27.5)	[126]

CKD: chronic kidney disease, DD: dialysis-dependent, DI: dialysis-independent, Hb: hemoglobin, SD: standard deviation

Indirect cost to patients for each IV iron infusion was calculated as 121 minutes per infusion multiplied by average hourly wage ($29.47) to estimate indirect cost.[127] The patient time for each RBC transfusion were approximated at four hours per transfusion.[128]

ESRD is associated with substantial indirect costs for both patients and caregivers. Table E14 outlines indirect cost inputs for ESRD. For DD-CKD patients, we attributed $10,752 per year to lost productivity of the patient and caregivers, an estimate from autosomal dominant polycystic kidney disease that includes unemployment, lost productivity, and caregiver lost productivity. Kidney transplants affected the patient, caregiver, and donor (if a living donor), and caregiver of the donor. Hours were multiplied by the average hourly wage ($29.47) to produce an indirect cost estimate.[124]

Table E14. Indirect Cost of ESRD

	Value	Source
DD-CKD, Including Patient and Caregiver	$10,752 per year	[129]
Transplant, Patient	252 hours of work lost	Assumed same value as donor
Transplant, Patient Caregiver	81 hours of work lost	Assumed same value as donor caregiver
Transplant, Donor	252 hours of work lost	[130]
Transplant, Donor Caregiver	81 hours of work lost	[130]
Transplant, Donor Caregiver	$1,193 (SD $1,968) in direct costs*	[130]

CKD: chronic kidney disease, DD: dialysis dependent, SD: standard deviation
*Original values inflated to 2020 USD.

Lastly, stroke and MI events were associated with an indirect cost due to lost productivity. Each stoke and MI event incurred 78.7 (SD 63.5) hours of lost productivity in the first month and 21.3 (SD 16.2) hours in subsequent cycles.[131] These lost productive hours were multiplied by the average hourly wage ($29.47) to produce an indirect cost estimate.[124]

AEs

Serious AEs other than MACE+ occurring in patients treated with roxadustat or ESAs were considered for inclusion. At present, the rate of non-MACE specific severe AEs in the DI-CKD population is unclear. In the DD-CKD population, one study (PYRENEES) presented the event rate per 100 person-years for severe AEs occurring in ≥1% of patients in any treatment group. In the

absence of any other data on severe AEs from other studies, those occurring in ≥5% of patients in either arm of PYRENEES were applied to both the DI-CKD and DD-CKD population as a constant per-cycle probability. Following this rule, only serious pneumonia was included.

Table E15. Serious Non-MACE AEs Occurring in ≥5% of Patients in any Treatment Group (PYRENEES)

	Roxadustat Event Rate per 100 Person-Years	ESA Event Rate per 100 Person-Years	Source
Pneumonia	2.3	2.9	[50]

ESA: erythropoiesis-stimulating agent

Table E16. AE Cost and Utility Inputs

Input	Value	Source
Cost of Pneumonia	$10,655 (95% CI $9,737, $11,708)	[132]
Disutility of Pneumonia (1 Cycle)	-0.0709 ± 0.020	[133]

CI: confidence interval

*Value inflated to 2020 USD.

Subgroup Analyses

ESA Normo-Responsive versus Hyporesponsive

Data regarding subgroups based on ESA-responsiveness for DOLOMITES are unavailable at the time of this report.

In the pooled roxadustat trials of HIMALAYAS, SIERRAS, and ROCKIES in the DD-CKD population, CFB in patients with inflammation and without inflammation (as a marker for responsiveness) were consistent with the overall outcomes.[57] However, patients who are ESA hyporesponsive may require higher doses to achieve correction of Hb levels. Based on real-world evidence, patients receiving dialysis who are ESA hyporesponders may require as much as a 3.8-fold higher ESA doses than normo-responders.[111] A scenario analysis was undertaken assuming higher and lower doses are needed in the DD-CKD population in hyporesponsive and normo-responsive patients, respectively.

Table E17. ESA Responsiveness Inputs (per Cycle)

Input	Base-Case Dose	Normoresponsive Dose	Hyporesponsive Dose	Source
Darbepoetin Alfa	160 mcg	100 mcg	240 mcg	Epoetin dose converted to darbepoetin[72]
Epoetin Alfa	52,682 units	24,331 units	94,831 units	[111]
Epoetin Beta	120 mcg	No information	No information	N/A

mcg: microgram

Iron Replete versus Non-Replete

No data regarding subgroups based on iron status for DOLOMITES or the pooled analysis of DD-CKD trials are unavailable at the time of this report.

Incident Dialysis versus Stable Dialysis

In the pooled analysis of incident dialysis patients, mean CFB in Hb was similar to the overall population (LSM difference vs. ESAs of 0.22 [0.05, 0.40]).[59] The reduction in mean monthly IV iron use was slightly greater in the incident-dialysis subpopulation relative to the overall pooled analysis -40.8 (-77.3, -4.3).[59] As described in the Subgroup Analyses and Heterogeneity section of the main report, no information was available at the time of this report for the subgroup with stable (non-incident dialysis), we were unable to complete the analysis stratified by these subgroups.

Comorbid Cardiovascular Disease

No data were identified from the roxadustat trials to inform relative impact on outcomes in patients with and without existing comorbid cardiovascular disease.

Comorbid Malignancy

No data were identified from the roxadustat trials to inform relative impact on outcomes in patients with and without existing comorbid malignancy.

E3. Results

Description of evLYG Calculations

The cost per evLYG considers any extension of life at the same "weight" no matter what treatment is being evaluated. Below are the stepwise calculations used to derive the evLYG.

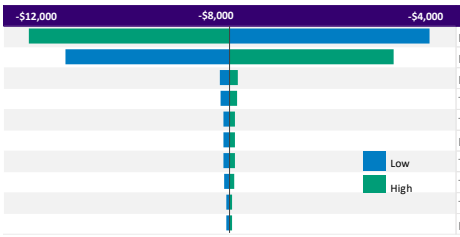
1. First, we attribute a utility of 0.851, the age- and gender-adjusted utility of the general population in the US that are considered healthy.[134]
2. For each cycle (Cycle I) in the model where using the intervention results in additional years of life gained, we multiply this general population utility with the additional LYs gained (ΔLYG).
3. We sum the product of the LYs and average utility (cumulative LYs/cumulative QALYs) for Cycle I in the comparator arm with the value derived in Step 2 to derive the evLY (evLY) for that cycle.
4. If no LYs were gained using the intervention versus the comparator, we use the conventional utility estimate for that Cycle I.

5. The total evLY is then calculated as the cumulative sum of QALYs gained using the above calculations for each arm.
6. We use the same calculations in the comparator arm to derive its evLY.
7. Finally, the evLYG is the incremental difference in evLY between the intervention and the comparator arms.

E4. Sensitivity Analyses

One-way sensitivity analyses were conducted for the outcome of total incremental cost in each population. In the DI-CKD population (Figure E1), the cost of roxadustat was by far the most impactful parameter on total incremental cost versus ESAs. In the DD-CKD population (Figure E2), the impact on all-cause mortality, stroke, and MI were the most impactful parameters, followed by cost of roxadustat and ESAs.

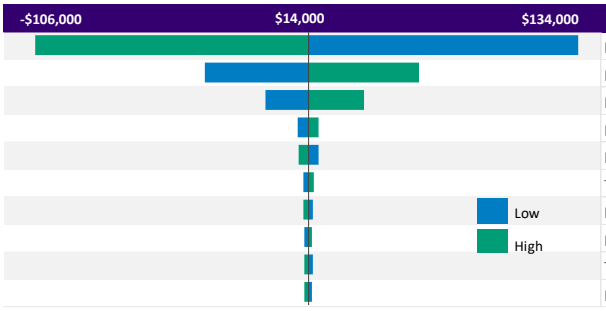
Figure E1. Tornado Diagram, DI-CKD, Commercial, One-Way Sensitivity Analysis of Incremental Cost



Parameter	Base Case	Low Value	High Value	Range	Low Result	High Result	Δ
Direct cost of ESAs, DI-CKD	$609.42	$548.48	$670.37	±10%	-$3,644	-$12,316	$8,672
Direct cost of roxadustat, DI-CKD	$498.71	$448.84	$548.59	±10%	-$11,528	-$4,432	$7,096
HR for mortality post-stoke & MI, DI-CKD	4.15	3.30	5.23	95% CI	-$8,178	-$7,799	$379
Transition probability Stage IV to death	0.080	0.072	0.1	±10%	-$8,166	-$7,811	$355
Transition probability Stage IIIb to death	0.041	0.037	0.0	±10%	-$8,114	-$7,853	$261
Discount rate for costs	0.23%	0.21%	0.0	±10%	-$8,105	-$7,858	$247
Transition probability Stage IIIb to IV	0.137	0.123	0.2	±10%	-$8,109	-$7,864	$245
Transition probability Stage IV to Stage V	0.081	0.073	0.1	±10%	-$8,098	-$7,869	$229
Transition probability Stage V to DD-CKD	0.626	0.563	0.7	±10%	-$8,050	-$7,918	$132
Risk of MI, ESAs, DI-CKD	0.27%	0.2%	0.3%	±10%	-$8,042	-$7,920	$121

DD-CKD: dialysis-dependent chronic kidney disease, DI-CKD: dialysis-independent chronic kidney disease, ESA: erythropoiesis-stimulating agent, HR: hazard ratio, MI: myocardial infarction

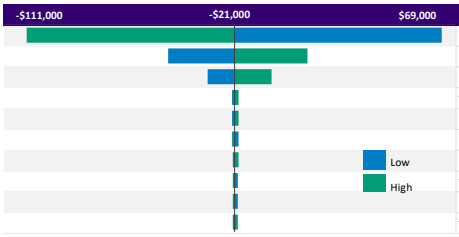
Figure E2. Tornado Diagram, DD-CKD, Commercial, One-Way Sensitivity Analysis of Incremental Cost



Parameter	Base Case	Low Value	High Value
RR for all-cause mortality vs ESAs, DD-CKD	1.05	0.88	1.26
RR for MI vs ESAs, DD-CKD	0.95	0.73	1.23
RR for stroke vs ESAs, DD-CKD	0.90	0.60	1.34
Direct cost of roxadustat, DD-CKD	$498.71	$448.84	$548.59
Direct cost of ESAs, DD-CKD	$465.59	$419.04	$512.15
Transition probability DD-CKD to death	0.154	0.138	0.2
Direct cost of transplant event	$19,636	$17,672	$21,600
Discount rate for costs	0.23%	0.21%	0.0
Transition probability DD-CKD to transplant	0.035	0.032	0.0
Direct cost of DD-CKD	$6,902	$6,212	$7,592

DD-CKD: dialysis-dependent chronic kidney disease, ESA: erythropoiesis-stimulating agent, MIL myocardial infarction, RR: risk ratio

Figure E3. Tornado Diagram, DD-CKD, Medicare, One-Way Sensitivity Analysis of Incremental Cost



Parameter	Base Case	Low Value	High Value	Range	Low Result	High Result	Δ
RR for all-cause mortality vs ESAs, DD-CKD	1.05	0.88	1.26	95% CI	$69,350	-$111,479	$180,829
RR for MI vs ESAs, DD-CKD	0.95	0.73	1.23	95% CI	-$49,654	$10,778	$60,432
RR for stroke vs ESAs, DD-CKD	0.90	0.60	1.34	95% CI	-$32,645	-$4,849	$27,796
Transition probability DD-CKD to death	0.154	0.138	0.2	±10%	-$21,980	-$19,152	$2,827
Direct cost of roxadustat, DD-CKD	$498.71	$448.84	$548.59	±10%	-$21,920	-$19,118	$2,802
Direct cost of transplant event	$19,636	$17,672	$21,600	±10%	-$19,128	-$21,911	$2,783
Discount rate for costs	0.23%	0.21%	0.0	±10%	-$21,789	-$19,324	$2,465
Transition probability DD-CKD to transplant	0.035	0.032	0.0	±10%	-$19,386	-$21,624	$2,238
Direct cost of DD-CKD	$6,902	$6,212	$7,592	±10%	-$19,402	-$21,637	$2,235
Years until included in the bundled payment	3.0	2.7	3.3	±10%	-$21,542	-$19,567	$1,975

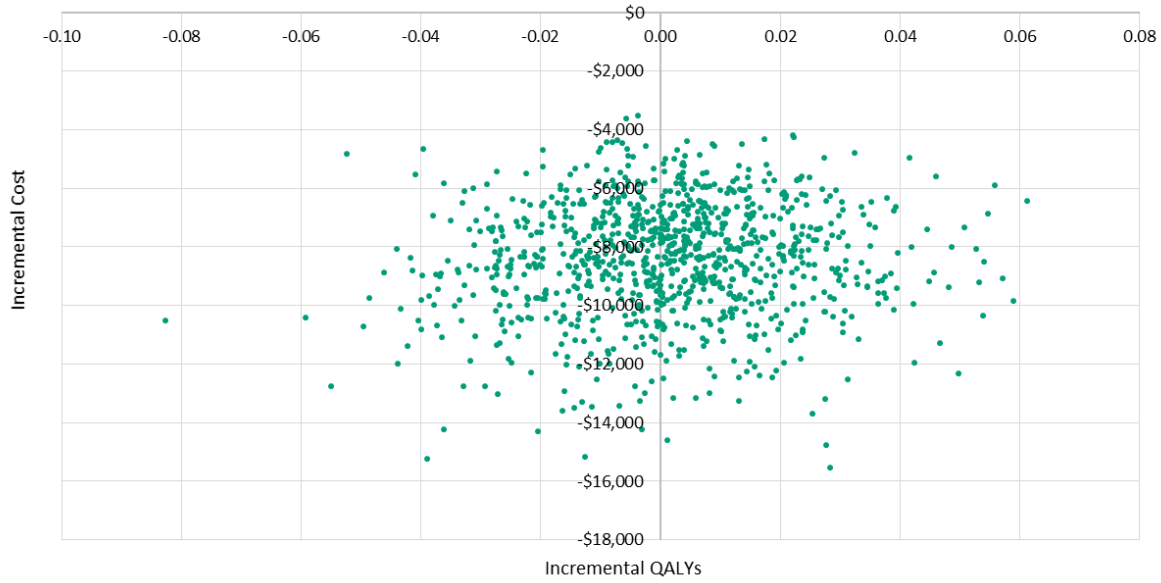
DD-CKD: dialysis-dependent chronic kidney disease, ESA: erythropoiesis-stimulating agent, MI: myocardial infarction, RR: risk ratio.

Table E18. Results of Probabilistic Sensitivity Analysis for Roxadustat versus ESAs

	Roxadustat		ESAs		Incremental	
	Mean	**Credible Range**	**Mean**	**Credible Range**	**Mean**	**Credible Range**
DI-CKD						
Total Costs	$429,000	($312,000, $582,000)	$437,000	($319,000, $592,000)	-$8,000	(-$13,000, -$5,000)
Total QALYs	5.5	(4.1, 7.2)	5.5	(4.1, 7.2)	0.00	(-0.04, 0.04)
DD-CKD, Commercial						
Total Costs	$859,000	($396,000, $1,615,000)	$865,000	($487,000, $1,550,000)	-$5,000	(-$329,000, $317,000)
Total QALYs	3.9	(1.9, 6.5)	3.9	(2.3, 6.2)	-0.07	(-1.35, 1.28)
DD-CKD, Medicare						
Total Costs	$1,031,000	($505,000, $1,712,000)	$1,040,000	($598,000, $1,657,000)	-$8,000	(-$426,000, $382,000)
Total QALYs	3.9	(1.9, 6.5)	3.9	(2.3, 6.2)	-0.07	(-1.35, 1.28)

CKD: chronic kidney disease, DD: dialysis-dependent, DI: dialysis-independent, ESA: erythropoiesis-stimulating agent, QALY: quality-adjusted life year

Figure E4. Probabilistic Sensitivity Analysis Results: Cost-Effectiveness Cloud for Incremental Cost and QALYs for Roxadustat vs. ESAs, DI-CKD, Commercial Perspective

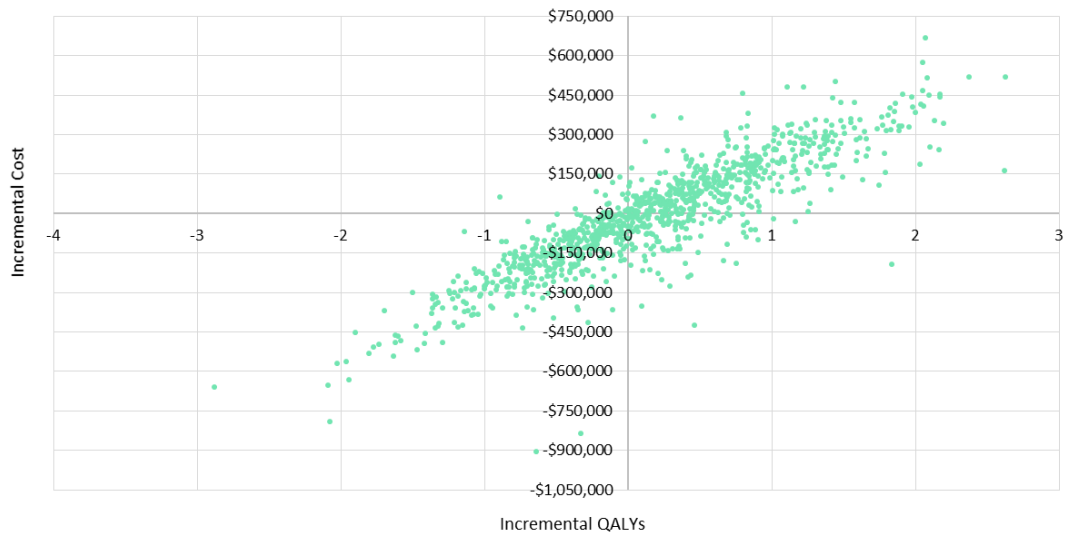


QALY: quality-adjusted life year

Figure E5. Probabilistic Sensitivity Analysis Results: Cost-Effectiveness Cloud for Incremental Cost and QALYs for Roxadustat vs. ESAs, DD-CKD, Commercial Perspective

QALY: quality-adjusted life year

Figure E6. Probabilistic Sensitivity Analysis Results: Cost-Effectiveness Cloud for Incremental Cost and QALYs for Roxadustat vs. ESAs, DD-CKD, Medicare Perspective



QALY: quality-adjusted life year

E5. Scenario Analyses

Scenario 1: Modified Societal Perspective

We conducted a modified societal perspective scenario analysis to include indirect costs of anemia, anemia treatment, CKD, and MACE+ summarized in above.

Table E19. Results for Modified Societal Perspective Scenario

Treatment	Drug Cost	Total Cost	Life Years	QALYs	evLYs
DI-CKD					
ESAs	$52,000	$580,000	7.40	5.21	5.21
Roxadustat	$44,000	$571,000	7.40	5.21	5.21
Incremental*	-8,000	-$9,000	0.00	<0.01	<0.01
DD-CKD, Commercial					
ESAs	$28,000	$1,150,000	6.16	3.72	3.72
Roxadustat	$29,000	$1,120,000	6.00	3.64	3.64
Incremental*	$1,000	-$28,000	-0.17	-0.08	-0.08
DD-CKD, Medicare					
ESAs	$0	$1,288,000	6.16	3.72	3.72
Roxadustat	$14,000	$1,269,000	6.00	3.64	3.64
Incremental*	$14,000	-$20,000	-0.17	-0.08	-0.08

DD-CKD: dialysis-dependent chronic kidney disease, DI-CKD: dialysis-independent chronic kidney disease, ESA: erythropoiesis-stimulating agent, evLY: equal-value life year, LY: life year, QALY: quality-adjusted life year
*Rounding within treatment-specific findings may produce differences when compared to the incremental findings.

Scenario 2: Inclusion of Impact on MACE+ in DI-CKD Population

We conducted a scenario including a potential impact on MACE+ versus ESAs based on the point estimates in the DOLOMITES trial. In this scenario, roxadustat resulted in 0.46 more QALYs due to reduction in mortality and MACE at an incremental cost of $24,000 versus ESAs higher cost ($24,000) compared with ESAs. Higher costs were driven by the potential reduction in mortality with roxadustat combined with CKD health state costs. When considering the uncertainty around the point estimates for all-cause mortality in DOLOMITES (HR=0.83, 95% CI 0.50, 1.38), the resulting incremental QALYs could range from 1.20 additional QALYs gained using the lower bound of the 95% CI to 0.37 fewer QALYs gained using the upper bound of the 95% CI.

Table E20. Scenario Analysis Inputs for Inclusion of Impact on MACE+ in DI-CKD Population

Parameter	Input (95% CI)	Source
RR for All-Cause Mortality for Roxadustat vs. ESAs	0.83 (0.50, 1.38)	[67]
RR for Stroke for Roxadustat vs. ESAs	0.48 (0.14, 1.67)	[67]
RR for MI for Roxadustat vs. ESAs	0.96 (0.41, 2.27)	[67]
RR for Unstable Angina Hospitalization for Roxadustat vs. ESAs	1.00 (1, 1)	[67]
HR for CHF Hospitalization for Roxadustat vs. ESAs	1.08 (0.6, 1.95)	[67]

CHF: congestive heart failure, CI: confidence interval, DI-CKD: dialysis-independent chronic kidney disease, ESA: erythropoiesis-stimulating agent, HR: hazard ratio, MACE+: major cardiovascular event, MI: myocardial infarction

Table E21. Results for Scenario Analysis of Inclusion of Impact on MACE+ in the DI-CKD Population

Treatment	Drug Cost	Total Cost	Life Years	QALYs	evLYs
ESAs	$52,000	$416,000	7.40	5.21	5.21
Roxadustat	$48,000	$443,000	8.07	5.69	5.81
Incremental*	-$4,000	$27,000	0.67	0.48	0.60

DI-CKD: dialysis-independent chronic kidney disease, ESA: erythropoiesis-stimulating agent, evLY: equal-value life year, LY: life year, MACE+: major cardiovascular event, QALY: quality-adjusted life year

*Rounding within treatment-specific findings may produce differences when compared to the incremental findings.

Scenario 3: Exclusion of Impact on MACE+ in DD-CKD Population

We conducted a scenario excluding any potential impact on MACE+ versus ESAs in the DD-CKD population due to uncertainty in the pooled estimates and lack of statistical significance of the individual MACE+ events.

Table E22. Results for Scenario Analysis of Exclusion of Impact on MACE+ in the DD-CKD Population

Treatment	Drug Cost	Total Cost	Life Years	QALYs	evLYs
Commercial Perspective					
ESAs	$28,000	$808,000	6.16	3.72	3.72
Roxadustat	$30,000	$809,000	6.16	3.74	3.74
Incremental*	$2,000	$1,500	0.00	0.01	0.01
Medicare Perspective					
ESAs	$0	$948,000	6.16	3.72	3.72
Roxadustat	$14,000	$962,000	6.16	3.74	3.74
Incremental*	$14,000	$14,000	0.00	0.01	0.01

DI-CKD: dialysis-independent chronic kidney disease, ESA: erythropoiesis-stimulating agent, evLY: equal-value life year, LY: life year, MACE+: major cardiovascular event, QALY: quality-adjusted life year

*Rounding within treatment-specific findings may produce differences when compared to the incremental findings.

E6. Heterogeneity and Subgroups

ESA Normo-Responsive vs. Hyporesponsive

Table E23. Results for Subgroup Analysis of ESA Normo-Responsive vs. Hyporesponsive, DD-CKD Population, Commercial Perspective

Treatment	Drug Cost	Total Cost	Life Years	QALYs	evLYs
Normo-Responsive					
ESAs	$16,000	$795,000	6.16	3.72	3.72
Roxadustat	$30,000	$779,000	6.00	3.64	3.64
Incremental*	$14,000	-$17,000	-0.17	-0.08	-0.08
Hyporesponsive					
ESAs	$46,000	$825,000	6.16	3.72	3.72
Roxadustat	$29,000	$8779,000	6.00	3.64	3.64
Incremental*	-$16,000	-$47,000	-0.17	-0.00	-0.00

DD-CKD: dialysis-dependent chronic kidney disease, ESA: erythropoiesis-stimulating agent, evLY: equal-value life year, LY: life year, QALY: quality-adjusted life year

*Rounding within treatment-specific findings may produce differences when compared to the incremental findings.

E7. Model Validation

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report (and Supplemental Materials). We also conducted sensitivity analyses with null input values to ensure the model was producing findings consistent with expectations. Further, independent modelers tested the mathematical functions in the model as well as the specific inputs and corresponding outputs.

Model validation was also conducted in terms of comparisons to other model findings. We searched the literature to identify models that were like our analysis, with comparable populations, settings, perspective, and treatments.

Prior Economic Models

A review of the literature for prior economic models was conducted comparing the cost effectiveness of ESAs or roxadustat treatments in CKD patients with anemia. We found nine peer reviewed publications, most of which (six) were outside the US.[66,135-141] Among studies comparing ESAs to other treatments in the US, Dahl et al. evaluated health outcomes and costs associated with ferumoxytol monotherapy, oral iron monotherapy, and in combination with ESAs in adult non-DD CKD patients.[140] The five-week treatment cost was $2,489, $5,216, $1,298, and $4,263 per patient for ferumoxytol, ferumoxytol with ESAs, oral iron, and oral iron with ESAs, respectively. The corresponding incremental costs per g/dL increase in Hb for ferumoxytol with ESAs, oral iron, and oral iron with ESAs, relative to ferumoxytol alone, was $398, $3,558, and $4,768 per patient. More recently, Yarnoff et al. used a CKD Health Policy Model to create a cohort of patients with CKD stages III-IV and explored the most cost-effective Hb target for anemia treatment.[66] They found that targeting a Hb between 10-11 g/dl resulted in an incremental cost-effectiveness ratios below $35,000/QALY, any treatment target above 11 g/dl increased medical costs and decreased QALYs. This study used a lifetime time horizon and health care sector perspective.

Only one study, Hu et al. evaluated roxadustat treatment for anemia in patients with CKD.[139] This study was performed in patients not receiving dialysis from perspective of the Chinese medical system. This study developed a Markov model with five-year time horizon to evaluate the cost effectiveness of roxadustat compared with placebo. QALY gains were entirely driven by elevation of Hb for roxadustat compared with placebo. Impact on CKD health states, mortality, and MACE were not considered. They found that roxadustat treatment (70 mg, three times per week) provided an additional 0.49 QALYs at a cost of $12,526 in the time horizon of five years, resulting in an incremental cost-effectiveness ratio of $25,563 per QALY. This study differs from our analysis due to the choice of comparator (placebo vs. ESAs). Other key differences include the cost of roxadustat ($21.20 USD three times per week, equating to $3,307 per year, approximately half of the placeholder price in our analysis) and health state utility derivation starting from the assumption of a 0.028 decrease in utility per 1 g/dL loss in Hb, more than twice that assumed in our analysis (0.0114).

F. Potential Other Benefits and Contextual Considerations

QALY Shortfalls

One important contextual consideration to consider is the argument that society should give preference to treatments for patients with more severe conditions,[142] and that giving priority to treatments according to "lifetime burden of illness" or "need" best represents the ethical instincts of a society or other decision-makers.[143,144] To inform this contextual consideration, ICER provides empirical results for the absolute QALY shortfall and proportional QALY shortfall. The absolute QALY shortfall is defined as the total absolute amount of future health patients with a condition are expected to lose without the treatment that is being assessed.[145] The ethical consequences of using absolute QALY shortfall to prioritize treatments is that conditions that cause early death or that have very serious lifelong effects on quality of life receive the greatest prioritization. Thus, certain kinds of treatments, such as treatments for rapidly fatal conditions of children, or for lifelong disabling conditions, score highest on the scale of absolute QALY shortfall.

The proportional QALY shortfall is measured by calculating the proportion of the total QALYs of remaining life expectancy that would be lost due to untreated illness.[146,147] The proportional QALY shortfall reflects the ethical instinct to prioritize treatments for patients whose illness would rob them of a large percentage of their expected remaining lifetime. As with absolute QALY shortfall, rapidly fatal conditions of childhood have high proportional QALY shortfalls, but the highest numbers can also often arise from severe conditions among the elderly who may have only a few years left of average life expectancy but would lose much of that to the illness without treatment.

For the DI-CKD population, the absolute shortfall was estimated to be 19.23 QALYs, with a proportional shortfall of 0.75, representing a loss of 75% of total quality-adjusted life expectancy (QALE) relative to individuals without the condition. For the DD-CKD population, the absolute shortfall was estimated to be 20.86 QALYs, with a proportional shortfall of 0.81, representing a loss of 81% of total QALE relative to individuals without the condition. To provide some anchoring of these results, we also present a league table of absolute and proportional QALY shortfalls for a variety of conditions from prior ICER reports (Table F1), using a burden of disease calculator developed by Dutch investigators (https://imta.shinyapps.io/iDBC/) that allows for calculation of absolute and proportional QALY shortfalls under different assumptions.[144]

Table F1. League Table of Absolute and Proportional QALY Shortfalls for Selected Conditions

	From ICER Reports			From iDBC tool[148]	
Condition	**Age**	**% Male**	**Total Undiscounted QALYs with Standard of Care**	**Absolute Shortfall**	**Proportional Shortfall**
DI-CKD	50	50%	6.52	19.23	0.75
DD-CKD	50	50%	4.89	20.86	0.81
Heterozygous FH with ASCVD	62	50	14.1	3.09	0.18
Secondary Prevention for ASCVD	66	61	13.9	0.54	0.04
Cystic Fibrosis	2	52	25.8	42.3	0.62
Secondary Progressive Multiple Sclerosis	48	39	3.0	24.5	0.89
Hemophilia A	18	100	38.6	13.3	0.26
Treatment-Resistant Major Depression	46	33	20.5	8.7	0.30
Moderate-to-Severe Ulcerative Colitis	40	59	27.4	6.2	0.19
BCG-Unresponsive High-Risk NMIBC	72	80	4.94	5.7	0.54

ASCVD: atherosclerotic cardiovascular disease, BCG: Bacillus Calmette-Guerin, FH: familial hypercholesterolemia, iDBC: Individual Driving Cycle Builder, NMIBC: non-muscular invasive bladder cancer, PTSD: post-traumatic stress disorder, QALY: quality-adjusted life year

G. Potential Budget Impact: Supplemental Information

Methods

ICER's methods for estimating potential budget impact are described in detail elsewhere and have recently been updated.[149] The intent of our revised approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy.

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential cost of using each new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over one- and five-year-time horizons. The five-year timeframe was of primary interest, given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of patients treated with the new therapy.

Using this approach to estimate potential budget impact, we then compared our estimates to an updated budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility. As described in ICER's methods presentation (https://icer.org/our-approach/methods-process/value-assessment-framework/) this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug approvals by the FDA over the most recent two-year period, and the contribution of spending on retail and facility-based drugs to total health care spending.

For 2019-2020, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $819 million per year for new drugs.

H. Public Comments

This section includes summaries of the public comments prepared for the CTAF Public Meeting on Thursday, February 11. These summaries were prepared by those who delivered the public comments at the meeting and are presented in order of delivery. Three speakers did not submit summaries of their public comments.

A video recording of all comments can be found here. Conflict of interest disclosures are included at the bottom of each statement for each speaker who is not employed by a pharmaceutical manufacturer.

Dustin Little, MD, AstraZeneca
Global Clinical Lead, Renal

Roxadustat is a first-in-class oral hypoxia-inducible factor prolyl hydroxylase (HIF-PH) inhibitor for adult patients with anemia of chronic kidney disease (CKD) on and not on dialysis. Roxadustat is based on Nobel Prize winning science, and the roxadustat global Phase III development program is one of the largest CKD anemia programs ever conducted, consisting of more than 8000 patients treated in six pivotal trials.

Anemia affects nearly all patients with dialysis-dependent CKD and is also common in patients with severe dialysis-independent CKD, yet there have been few advances in CKD anemia care in over 30 years. Erythropoiesis-stimulating agents (ESAs) are the cornerstone of CKD anemia management, however their parenteral route of administration can be a barrier for some patients, and they don't address impaired iron utilization, which is a major contributor to the pathophysiology of CKD anemia.

Roxadustat is an oral medication that induces endogenous erythropoietin production and increases iron utilization, thereby reducing the requirement for intravenous iron and decreasing RBC transfusion risk. Reduction in transfusion risk is key for many patients with advanced CKD, because transfusion may reduce the likelihood of transplantation. Increased access to transplantation is critical in CKD, because transplantation is associated with improved survival and increased quality of life, and because substantial kidney transplant disparities exist in the United States, with Black patients being half as likely to undergo kidney transplantation, despite being four times as likely to have kidney disease.

AstraZeneca and FibroGen support patient-centric value assessments that take into consideration innovative therapies that address unmet medical need. However, we feel that ICER's analysis is not yet complete. Notably, the roxadustat pivotal trials and pooled analyses were not yet published in

peer-reviewed medical journals at the time of ICER's analysis. Although some results have since been published, this precluded a fully informed examination of the value of roxadustat.

This is apparent in ICER's evaluation of roxadustat's value in the dialysis-dependent population. To assess mortality, ICER have used results from a meta-analysis they performed, which yielded an ACM risk ratio point estimate of 1.05 (with 95% CI crossing 1.0). However, the pooled ACM HR for roxadustat vs. epoetin alfa in the three pivotal dialysis dependent studies has a point estimate of <1.0. These results have been accepted for publication in a major peer-reviewed medical journal. Additionally, the roxadustat global Phase III program was designed to enable a rigorous prospective assessment of cardiovascular safety for roxadustat compared to ESA in incident dialysis patients. These patients were enrolled during the incident dialysis period and followed into the prevalent dialysis period, with mean roxadustat exposure of approximately 1.5 years. This is highly clinically relevant, because anemia therapy in the United States is generally initiated in conjunction with dialysis initiation and continued chronically. Importantly, in the pooled incident dialysis population from the global Phase III roxadustat program, roxadustat-treated patients had a 30% lower risk of MACE and a 34% lower risk of MACE+. These results have recently been published by a peer-reviewed medical journal.

In addition to the limitations above, the present evaluation is limited by failure to not consider the pending guidance on eligibility and reimbursement for roxadustat via the Transitional Drug Add-on Payment Adjustment (TDAPA) payment system.

Overall, we believe that roxadustat offers value as an oral treatment that reduces the risk of transfusion, decreases the requirement for intravenous iron, and effectively treats anemia in dialysis-independent and dialysis-dependent patients, with consistent efficacy across subgroups that persisted over mean treatment durations with roxadustat of over 1.5 years. Effectively treating CKD anemia and lowering transfusion risk with an oral therapy that does not require parenteral administration in health-care settings, and that decreases the need for IV iron, should minimize disruption of work and family life for patients and caregivers. This may be particularly important for historically disadvantaged and underserved communities, who may be more likely to have employment instability, increased caregiver responsibilities for family members, and decreased flexibility with work schedules. Additionally, roxadustat has been shown to have no increased cardiovascular risk compared to placebo in dialysis-independent CKD, decreased risk for MACE and MACE+ compared to ESA in incident dialysis patients, and decreased MACE+ risk compared to ESA in the overall dialysis population.

In summary, roxadustat is an innovative therapy with a distinct mechanism of action, that is administered orally, and that offers advantages over currently available treatments in a disease area with high unmet medical need and little advancement in over 30 years.

Jeffrey Petersen, MD, Amgen
Global Development Lead

Amgen is deeply committed to patients suffering from anemia in chronic kidney disease (CKD). Over the past 30 years we have continued to improve our understanding of the benefits and risks of ESAs for patients with anemia due to CKD through evidence-based medicine principles, which includes, but is not limited to, the conduct of prospective randomized controlled trials, label revisions, reimbursement, and the review of real-world data. We believe there is significant uncertainty around the Revised Report and we advise ICER to incorporate the below recommendations to more accurately capture value in the Final Report:

The evidence used to assess efficacy and cardiovascular safety are inconclusive, yet the Revised Report continued with the pooled analysis without the PYRENEES study.

- Cardiovascular Safety: ICER's report minimizes uncertainties about roxadustat's impact on safety compared to ESAs. The confidence intervals related to cardiovascular safety, MACE/MACE+, include the possibility of large clinically important harms or benefits. Two recent publications, of the incident subset defined as 1) incident dialysis population and 2) the non-dialysis population, along with accompanying commentary adds to the substantial uncertainties in ICER's long-term cost-effectiveness analysis. Our points emanate from the commentary on these publications which highlights that 40% of non-dialysis patients were iron deficient at baseline and that oral iron was "encouraged," but administering intravenous iron was considered rescue therapy. In addition, the sub-group analysis of the incident dialysis population is hypothesis-generating and by no means definitive. Lastly, longer follow-up of real-world patients is necessary to learn about any uncommon or late-term adverse or beneficial effects.

- Efficacy: In addition, the above-mentioned commentary also noted that roxadustat proved to be non-inferior to Epogen® with different protocolized dosing algorithms in the two arms in the incident dialysis population. There was no statistically significant difference in QALYs between roxadustat and ESAs for the dialysis-independent (DI) CKD population, perhaps more importantly, fewer QALYs were generated for roxadustat in the dialysis dependent (DD) CKD population versus ESAs.

- Cost-minimization: The Revised Report performed a cost-minimization exercise which relies on a flawed core assumption – cost savings to health systems are due to higher mortality rates for dialysis patients on roxadustat. The model's cost-savings are primarily attributable to more dialysis patients on roxadustat dying, thus no longer incurring healthcare costs. Therefore, it is unknown whether roxadustat saves costs or adds costs. The Final Report should convey the need for treatments where value rests not only in reduced healthcare system costs but improved patient outcomes.

Thus, the Final Report should be revised to reflect the high level of uncertainty in roxadustat's results. At a minimum, ICER should highlight:

- Additional data and longer follow-up of real-world patients is necessary to learn about any uncommon or late-term adverse or beneficial effects. We advise ICER to revise the analysis so higher mortality does not result in cost-savings and reinforce the position that few hard conclusions can be made in their Final Report.

I. Meeting Participants and Conflict of Interest Disclosures

Tables I1 through I3 contain conflict of interest (COI) disclosures for all participants at the Thursday, February 11 Public Meeting of CTAF.

Table I1. ICER Staff and Consultants

ICER Staff and Consultants	
Foluso Agboola, MBBS, MPH,* Vice President of Research, ICER	**Grace Fox, PhD,*** Research Lead, ICER
Lisa Bloudek, PharmD, MS,* Senior Research Scientist, University of Washington	**Reem Mustafa, MD, MPH, PhD,*** Associate Professor of Medicine; Director, Outcomes and Implementation Research, University of Kansas Medical Center
Jonathan D. Campbell, PhD, MS,* Senior Vice President for Health Economics, ICER	**Steven D. Pearson, MD, MSc,*** President, ICER
Josh J. Carlson, PhD, MPH,* Associate Professor, Department of Pharmacy, University of Washington	**David M. Rind, MD, MSc,*** Chief Medical Officer, ICER
Laura Cianciolo,* Program Manager, ICER	**Azanta Thakur,*** Program and Event Coordinator, ICER
Noemi Fluetsch, MPH,* Research Assistant, Health Economics and Outcomes Research, ICER	

*No conflicts of interest to disclose, defined as individual health care stock ownership (including anyone in the member's household) in any company with a product under study, including comparators, at the meeting in excess of $10,000 during the previous year, or any health care consultancy income from the manufacturer of the product or comparators being evaluated.

Table I2. Policy Roundtable Participants and COI Disclosures

Policy Roundtable Participant	Conflicts of Interest
Jeffrey S. Berns, MD, Professor of Medicine; Associate Chief, Renal Electrolyte and Hypertension, University of Pennsylvania	No conflicts of interest to disclose.
Kerry Cooper, PharmD, Vice President of US Renal Medical Affairs, AstraZeneca	Full-time employee of AstraZeneca.
Leslie Fish, RPh, PharmD, Vice President, IPD Analytics	Full-time employee of IPD Analytics.
Yola Gawlik, MHA, Executive Director, US Government Affairs and Policy, Amgen	Full-time employee of Amgen.
Patrick O. Gee, Sr., PhD, JLC, Founder and CEO, iAdvocate, Inc.	No conflicts of interest to disclose.
Pinelopi Kapitsinou, MD, Associate Professor of Medicine, Division of Nephrology and Hypertension, Northwestern University, Feinberg School of Medicine	Dr. Kapitsinou owns stock in excess of $10,000 in Biogen, Merck, and Pfizer.
Rosalie Patel, PharmD, Principal Pharmacist, Formulary Strategy and Management	Rosalie Patel is a full-time employee of Blue Shield of California.
Troy Zimmerman, Vice President, Government Relations, National Kidney Foundation	NKF receives more than 25% of its revenue from health care and life sciences companies.

Table I3. CTAF Panel Member Participants and COI Disclosures

Participating Members of CTAF	
Ralph G. Brindis, MD, MPH, MACC, FSCAI, FAHA,* Clinical Professor of Medicine, UCSF	**Elizabeth J. Murphy, MD, DPhil,*** Professor of Clinical Medicine, UCSF; Chief, Division of Endocrinology and Metabolism, Zuckerberg San Francisco General Hospital
Robert Collyar,* Patient Advocate; Board Member, Breast Cancer Action; Co-Founder, Clinical Trials Information Project	**Kathryn A. Phillips, PhD,*** Professor of Health Economics and Health Services Research; Director and Founder, UCSF Center for Translational and Policy Research on Personalized Medicine; Department of Clinical Pharmacy/School of Pharmacy, UCSF Institute for Health Policy Studies, and UCSF Comprehensive Cancer Center
Rena K. Fox, MD,* (Chair) Professor of Medicine, UCSF	**Ann Raldow, MD, MPH,*** Assistant Professor, Department of Radiation Oncology, UCLA David Geffen School of Medicine
Kimberly Gregory, MD, MPH,* Vice Chair of Women's Healthcare Quality and Performance Improvement, Department of Obstetrics and Gynecology; Director, Division of Maternal Fetal Medicine, Cedars-Sinai Medical Center	**Richard Seiden, JD,*** Patient Advocate, Retired Partner, Foley & Lardner LLP
Paul Heidenreich, MD, MS,* Professor and Vice-Chair for Quality, Clinical Affairs, and Analytics, Stanford University	**Alexander Smith, MD, MPH,*** Associate Professor of Medicine, UCSF
Jeffrey Hoch, PhD,* Associate Director, Center for Healthcare Policy and Research, UC Davis	**Joanna Smith, LCSW, MPH, CHA,*** Chief Executive Officer, Healthcare Liaison, Inc.
Sei Lee, MD,* Associate Professor of Medicine, Division of Geriatrics, UCSF	**Anthony Sowry,*** Patient Advocate and Lead Volunteer, California, National Patient Advocate Foundation; Senior Vice President, Maritime Container Shipping (Retired)
Joy Melnikow, MD, MPH,* Director, Center for Healthcare Policy and Research; Professor, Family and Community Medicine, University of California, Davis	

*No conflicts of interest to disclose, defined as individual health care stock ownership (including anyone in the member's household) in any company with a product under study, including comparators, at the meeting in excess of $10,000 during the previous year, or any health care consultancy income from the manufacturer of the product or comparators being evaluated.