



# **Treatments for Anemia in Chronic Kidney Disease: Effectiveness and Value**

**Evidence Report**

**January 28, 2021**

**Prepared for**



ICER Staff and Consultants	University of Washington Modeling Group
<p><b>Reem Mustafa, MD, MPH, PhD</b> Associate Professor of Medicine Director, Outcomes and Implementation Research University of Kansas Medical Center</p> <p><b>Grace Fox, PhD</b> Research Lead Institute for Clinical and Economic Review</p> <p><b>Jonathan D. Campbell, PhD, MS</b> Senior Vice President for Health Economics Institute for Clinical and Economic Review</p> <p><b>Foluso Agboola, MBBS, MPH</b> Vice President of Research Institute for Clinical and Economic Review</p> <p><b>Steven D. Pearson, MD, MSc</b> President Institute for Clinical and Economic Review</p> <p><b>David M. Rind, MD, MSc</b> Chief Medical Officer Institute for Clinical and Economic Review</p>	<p><b>Lisa Bloudek, PharmD, MS</b> Senior Research Scientist University of Washington</p> <p><b>Josh J. Carlson, PhD, MPH</b> Associate Professor, Department of Pharmacy University of Washington</p> <p><i>The role of the University of Washington is limited to the development of the cost-effectiveness model, and the resulting ICER report does not necessarily represent the views of the University of Washington.</i></p>

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*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](http://icerorg.wpengine.com/wp-content/uploads/2020/10/ICER_Anemia_in_CKD_Stakeholder_List_072020.pdf).

## **Expert Reviewers**

**Jeffrey S. Berns, MD**

**Professor of Medicine; Associate Chief, Renal Electrolyte and Hypertension  
University of Pennsylvania**

*No relevant conflicts of interest to disclose, defined as more than \$10,000 in health care company stock or more than \$5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.*

**Pinelopi Kapitsinou, MD**

**Associate Professor of Medicine, Division of Nephrology and Hypertension  
Northwestern University, Feinberg School of Medicine**

*No relevant conflicts of interest to disclose, defined as more than \$10,000 in health care company stock or more than \$5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.*

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## 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
MA	Meta-analysis
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

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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).<sup>1-4</sup> 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.<sup>5-7</sup>

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,<sup>8</sup> and the use of erythropoietin and related compounds collectively known as erythropoiesis-stimulating agents (ESAs) dramatically reduced the need for transfusions.<sup>9</sup> 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.<sup>10-</sup>

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Hypoxia-inducible factors 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.<sup>14,15</sup> The HIF-PH inhibitor roxadustat (AstraZeneca) is under review by the Food and Drug Administration (FDA) with an expected decision date in March 2021.

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,<sup>16</sup> 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 one key published Phase III RCT of roxadustat<sup>17</sup> and three key unpublished Phase III RCTs of roxadustat.<sup>18-21</sup> A pooled analysis of the three placebo-controlled trials reported no statistically significant differences in the risk of MACE (hazard ratio [HR]: 1.08; 95% confidence interval [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).<sup>16</sup> In the one 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).<sup>18</sup>

In the DD-CKD population, we also identified four key unpublished Phase III RCTs comparing roxadustat with ESAs.<sup>20-23</sup> 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).<sup>16</sup> 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 transfusion compared with placebo, but point estimates and confidence intervals raise the possibility of increases in MACE and mortality in a high-risk population. As such, we have rated roxadustat *promising but inconclusive* (“P/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. For similar reasons, in the DD-CKD population, we have *insufficient* evidence (I) for the comparison between roxadustat and ESAs.

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.

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.

# 1. Background

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Anemia is common in patients with chronic kidney disease (CKD), and hemoglobin (Hb) levels typically decline as CKD progresses.<sup>1,3</sup> 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.<sup>24,25</sup> 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.<sup>5-7</sup> 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.<sup>26-29</sup>

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.<sup>30,31</sup> 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.<sup>32</sup> 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.<sup>33</sup>

In patients with DI-CKD, the prevalence of anemia increases with decline in kidney function and advancing stages of CKD.<sup>1-3</sup> 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.<sup>4</sup> 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,<sup>8</sup> 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.<sup>9</sup> 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.<sup>10-13</sup> As a result, target Hb levels in patients with DD-CKD were reduced.<sup>9</sup>

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 factors (HIF) are transcription factors that regulate 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- $\alpha$  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) with an expected decision date in March 2021. 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

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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

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### 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,<sup>34</sup> 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 10 references relating to two RCTs comparing roxadustat to darbepoetin alfa<sup>18,35</sup> and eight RCTs comparing roxadustat to placebo<sup>17,19-21,36-39</sup> 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.<sup>17-19 20,21</sup> Only ANDES has been published, and data for the remaining trials 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 (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.<sup>18</sup> 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.<sup>20,21</sup> 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,<sup>21,23,38,40-43</sup> two RCTs in incident and stable DD-CKD,<sup>20,21</sup> and one RCT in incident DD-CKD<sup>21,22</sup> 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  $\leq 4$  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.<sup>20-23</sup> 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).<sup>20-22</sup> 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.<sup>21,23</sup> 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**

<b>Trials (No. of Patients)</b>	<b>Population</b>	<b>Primary Endpoint</b>	<b>Treatment Arms</b>	<b>Key Baseline Characteristics</b>
<b>DI-CKD</b>				
<b>DOLOMITES (616)</b>	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%
<b>ALPS (594)</b>	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: 36%
<b>ANDES (922)</b>	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%
<b>OLYMPUS (2781)</b>	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%
<b>DD-CKD§</b>				
<b>HIMALAYAS (1043)</b>	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%
<b>PYRENEES (836)</b>	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
<b>ROCKIES (2133)</b>	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
<b>SIERRAS (741)</b>	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  $\geq$ 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  $\geq$ 2.0 g/dL in patients with baseline Hb  $\leq$ 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.<sup>18</sup> There were no significant differences in the risk of MACE (hazard ratio [HR]: 0.81; 95% confidence interval [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.<sup>16</sup>

##### *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.<sup>18</sup> However, this difference did not exceed the MCID of 3 to 5 points.<sup>44</sup> 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).<sup>18</sup>

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.<sup>45</sup> However, MCIDs of 3 to 5 points were not reached in SF-36 PF or VT sub-scores in the pooled analysis.<sup>44</sup> Further, we performed meta-analyses of these outcomes averaged over weeks 12 to 28 reported for ALPS, ANDES, and OLYMPUS.<sup>17,19,46</sup> 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 D6 and Figure D7 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).<sup>47</sup>

### ***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.<sup>16</sup>

### ***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).<sup>18</sup>

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 D8 for additional details.

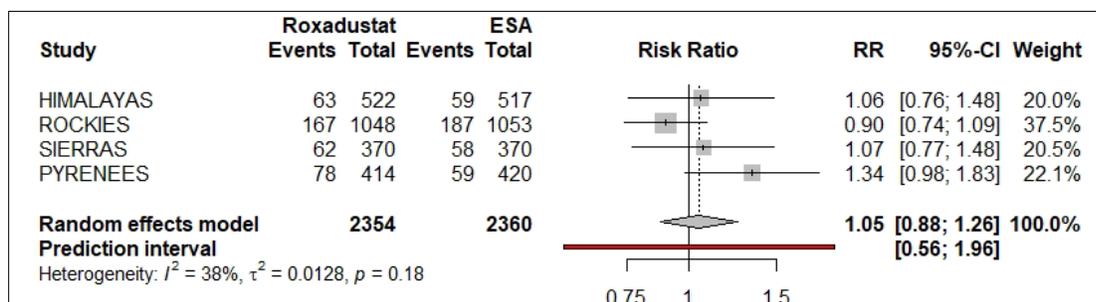
## DD-CKD

### 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.<sup>16</sup> However, the risk of MACE+ was reduced with roxadustat compared to epoetin alfa (HR: 0.86; 95% CI: 0.74 to 0.98).<sup>16</sup> 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).<sup>21</sup> 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 3.1, the meta-analysis found no significant difference between roxadustat and ESAs (risk ratio [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 3.1. 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,  $\tau^2$ : 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.<sup>46</sup> Notably, a MCID of 3 to 5 points was not reached in these assessments.<sup>44</sup>

### ***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).<sup>23</sup> Similar results for rescue therapy were reported for ROCKIES in the first 52 weeks (HR: 0.83; 95% CI: 0.64 to 1.07).<sup>21</sup>

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).<sup>16</sup>

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).<sup>21,48</sup>

### ***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 D14 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.<sup>49</sup> 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).<sup>18</sup> 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 placebo (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).<sup>21</sup> The most commonly reported TEAEs included kidney failure, decrease in eGFR, nausea, hyperkalemia, and hypertension.<sup>21</sup> 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 D15 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: 1.38; 95% CI: 1.02 to 1.88; see Figure D16 in the 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).<sup>21</sup> 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 D17 and Figure D18 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 D19 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 eight references for subgroup analyses of the key RCTs and pooled analysis.<sup>16,21,45,50-54</sup> 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 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.<sup>17</sup> 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.<sup>21,22,55</sup> 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.<sup>40,41</sup>

##### Incident-Dialysis Subgroup

We identified two references for subgroup analyses of incident DD-CKD patients.<sup>56,57</sup> 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.<sup>16</sup>

## 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 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.<sup>34</sup> 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.

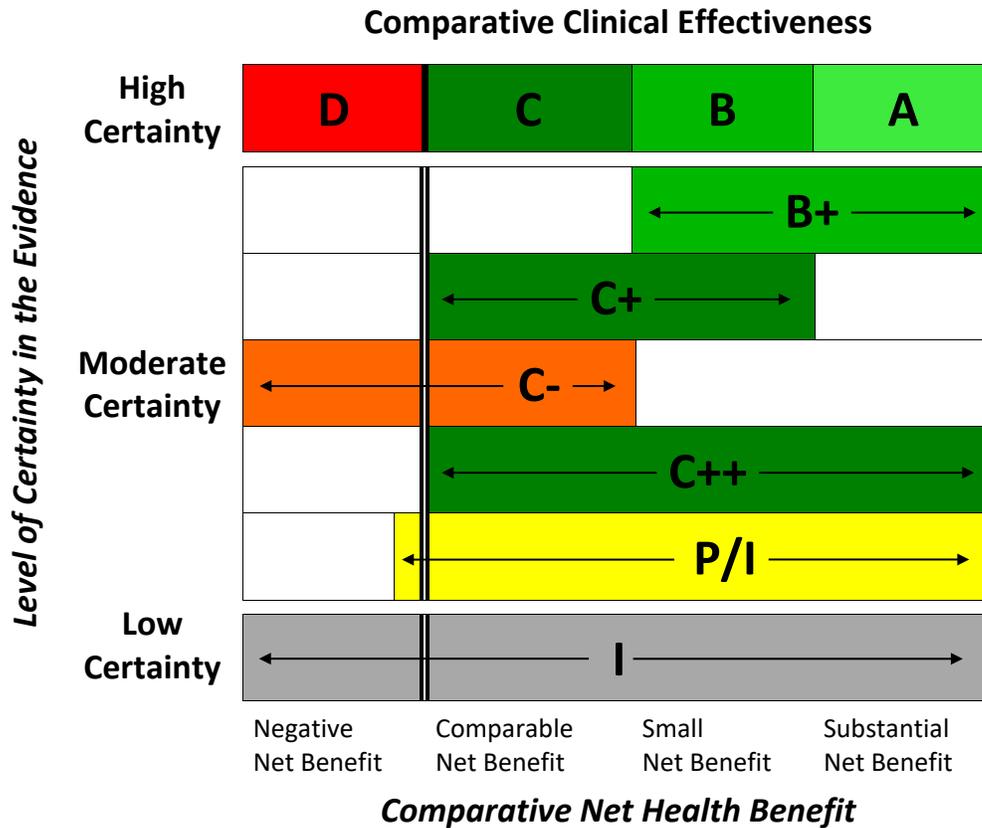
We acknowledge the differences in the use of rescue therapy between the treatment arms in the trials in which ESAs were used as part of the rescue therapy for the roxadustat arm. However, the limited available data hinder further exploration of the impact of these differences and the potential associated 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:

<https://icer.org/evidence-rating-matrix/>.

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 one key trial, ANDES, has been published, the remaining key trials (ALPS and OLYMPUS) have 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.

Though available data suggest no statistically significant difference between roxadustat and placebo (HR: 1.06; 95% CI: 0.91 to 1.23), 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 the DI-CKD population could range from one fewer to three additional deaths per 100 patients (timeframe up to four and a half years of treatment).

However, we note that rescue therapy, including with ESAs, was available and was used far more frequently in the placebo arms than in the roxadustat arms of the trials. As such, and given the results comparing roxadustat and ESAs, and the routine clinical choice to administer ESAs to patients with DI-CKD who would otherwise require transfusions, we feel that in such patients where ESAs are not available, roxadustat would likely provide a net clinical benefit despite the potential for harms.

In patients with DI-CKD who would otherwise require blood transfusions, we feel the evidence for roxadustat is *promising but inconclusive* ("P/I"). The P/I rating should be considered with caution as

it does not apply to patients with DI-CKD who would not require transfusions but have symptoms of anemia such as fatigue or exercise intolerance.

## 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
<b>DI-CKD</b>		
<b>Roxadustat</b>	ESAs (i.e., darbepoetin alfa)	Insufficient (I)
	Usual care (estimated by the placebo arms of clinical trials)	Promising but inconclusive (P/I)
<b>DD-CKD</b>		
<b>Roxadustat</b>	ESAs (i.e., epoetin alfa and darbepoetin alfa)	Insufficient (I)

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

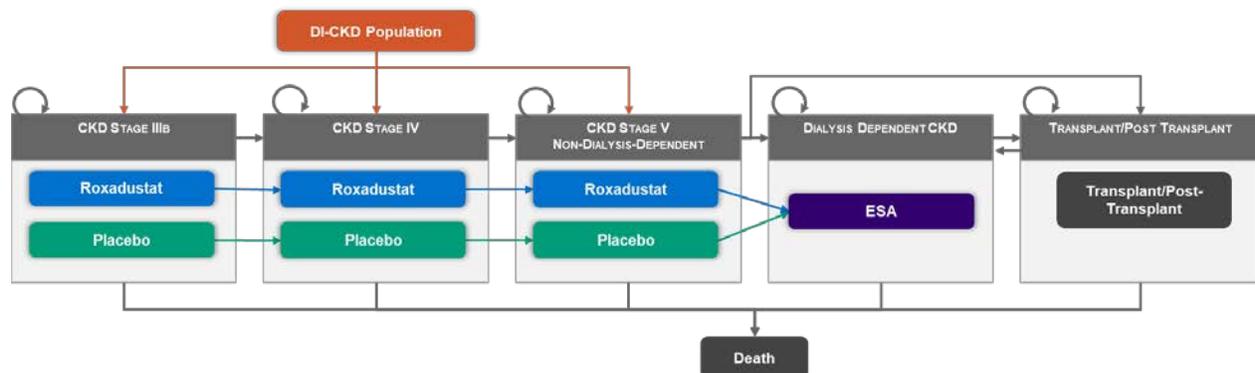
## 4. Long-Term Cost-Effectiveness

### 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.

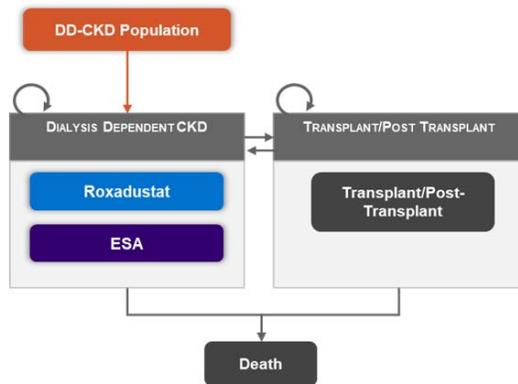
The model considered drug costs, administration costs, use of IV iron, serious adverse events, RBC transfusions, and MACE+. A modified societal perspective was undertaken as a scenario analysis, which included indirect costs due to lost productivity.

**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  $\geq 10$  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**

<b>Assumption</b>	<b>Rationale</b>
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. <sup>58</sup>
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.<sup>59</sup> 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.<sup>59</sup> 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 <sup>60</sup>
Baseline DI-CKD Stage IV/V without Anemia	0.72	Nguyen 2018; EQ-5D <sup>60</sup>
Baseline DD-CKD ESRD without Anemia	0.609 (0.566, 0.652)	Manns 2003; EQ-5D <sup>61</sup>
Utility Increase Post Transplant	0.13	Laupacis 1996; TTO <sup>62</sup>
Utility Loss per 1 g/dl Decrease in Hb (Reference Hb ≥13 g/dL)	0.0114	Finkelstein 2009; <sup>59</sup> SF-36 & mapping function from Ara 2008 <sup>63</sup> as cited in Yarnoff 2016 <sup>64</sup>

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).<sup>16,65</sup> 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 [Supplemental Table E20](#) and [Table E21](#) 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.<sup>16</sup> 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 MA
MI	5.3%	5.6%	0.95 (0.73, 1.23)	<sup>16</sup>
Stroke	2.3%	2.6%	0.90 (0.60, 1.34)	<sup>16</sup>
Unstable Angina	0.9%	1.1%	0.82 (0.44, 1.52)	<sup>16</sup>
CHF Hospitalization	6.2%	8.6%	0.72 (0.58, 0.91)	<sup>16,66</sup>

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, MA: meta-analysis, 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 [Supplemental 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 process (e.g., Parsabiv® [etelcalcetide]).<sup>67</sup>

## 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  $\geq 10$  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 \$8,220 in lifetime cost savings with roxadustat, which remained likely cost-saving in probabilistic sensitivity analysis (-\$9,100; 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	\$54,000	\$1,127	\$283	\$374,000	\$430,000	5.38	7.64	5.38
Roxadustat	\$46,000	\$1,021	\$283	\$374,000	\$422,000	5.38	7.64	5.38
Incremental†	-\$8,114	-\$106	\$0	\$0	-\$8,220	<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 -\$368,000 to \$329,000.

**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	\$29,000	\$4,588	\$357	\$800,000	\$834,000	3.84	6.35	3.84
Roxadustat	\$30,000	\$4,390	\$285	\$769,000	\$804,000	3.75	6.18	3.75
Incremental†	\$1,218	-\$197	-\$72	-\$31,000	-\$30,000	-0.09	-0.17	-0.09

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 $\geq$ 10 g/dL	RBC Transfusions	Strokes	MIs	Angina Hospitalizations	CHF Hospitalizations
ESAs	2.74	0.61	0.11	0.23	0.04	0.36
Roxadustat	3.74	0.49	0.09	0.22	0.04	0.34
Incremental*	0.99	-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 ( $\$6,500 \times 3$ ), 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	\$978,000	\$978,000
Roxadustat	\$14,000	\$0	\$0	\$942,000	\$957,000
Incremental‡	\$14,000	\$0	\$0	-\$36,000	-\$22,000

ESA: erythropoiesis-stimulating agent, IV: intravenous, RBC: red blood cell

\*Included in bundled payment as part of total cost of care.

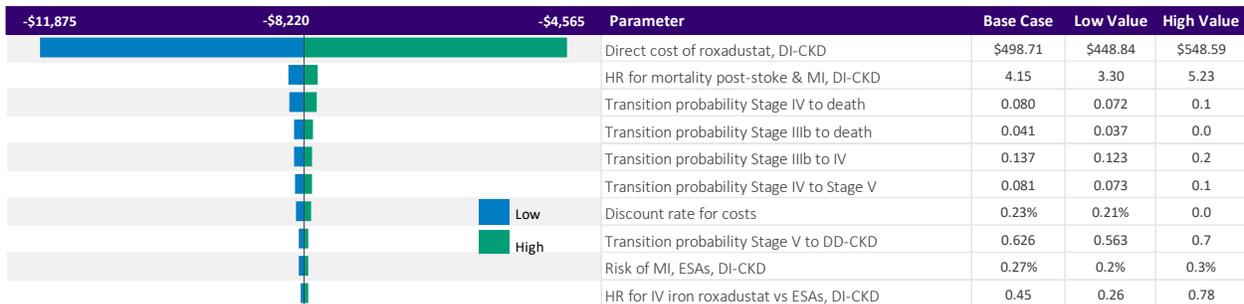
†Includes adverse events, MACE+, and cost of Medicare bundled payment.

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

## Sensitivity Analyses

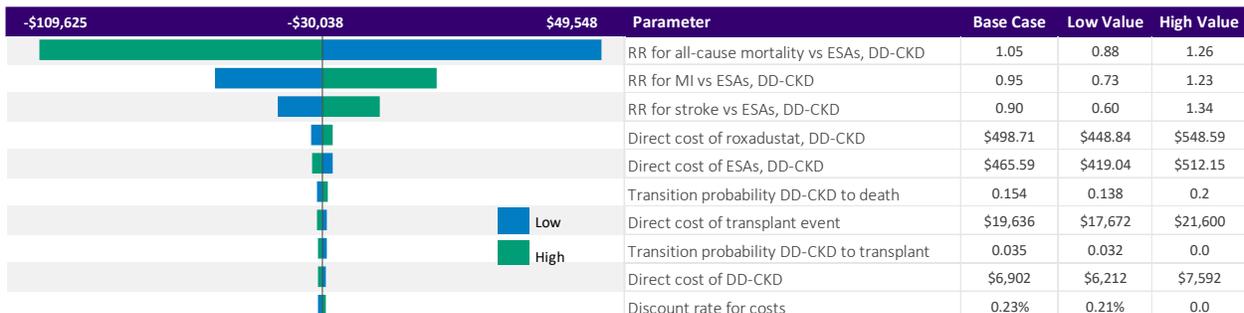
One-way sensitivity analyses (OWSAs) were conducted for the outcome of total incremental cost in each population. In the DI-CKD population (Figure 4.2), the cost of roxadustat was by far the most impactful parameter on total incremental cost versus ESAs. In the DD-CKD population (Figure 4.3), the impact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



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**



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 0.46 more QALYs at a higher cost (\$24,000) 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 1.15 additional QALYs gained using the lower bound of the 95% CI to 0.36 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	-\$8,220	-\$9,416	\$24,000
Incremental QALYs	<0.01	<0.01	0.46

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+
<b>Roxadustat vs. ESAs, Commercial Perspective</b>			
Incremental Cost	-\$30,000	-\$41,000	\$1,600
Incremental QALYs	-0.09	-0.09	0.01
<b>Roxadustat vs. ESAs, Medicare Perspective</b>			
Incremental Cost	-\$22,000	-\$32,000	\$14,000
Incremental QALYs	-0.09	-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 \$6,163 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 \$141 per year.

## **Model Validation**

Model validation is described in Section E7 of the 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 <a href="#">Report Supplement</a> 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 <a href="#">Report Supplement</a> 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

## 6. Health Benefit Price Benchmarks

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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.

# 7. Potential Budget Impact

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## 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<sup>68,69</sup>
  - 42.9% are stage III; 2.5% are stage IV; 0.9% are stage V<sup>69</sup>
  - Anemia prevalence by stage is: 17.4% for stage III; 50.4% for stage IV; 53.4% for stage V<sup>4</sup>; 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<sup>4</sup>

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.

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