Treatments for Anemia in Chronic Kidney Disease: Effectiveness and Value

Draft Evidence Report

November 30, 2020

Prepared for

CTAF
CALIFORNIA TECHNOLOGY
ASSESSMENT FORUM

AN ICER PROGRAM

ICER Staff and Consultants	University of Washington Modeling Group
Reem Mustafa, MD, MPH, PhD Associate Professor of Medicine Director, Outcomes and Implementation Research University of Kansas Medical Center	**Lisa Bloudek, PharmD, MS** Senior Research Scientist University of Washington
Grace Fox, PhD Research Lead Institute for Clinical and Economic Review	**Josh J. Carlson, PhD, MPH** Associate Professor, Department of Pharmacy University of Washington
Jonathan D. Campbell, PhD, MS Senior Vice President for Health Economics Institute for Clinical and Economic Review	*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.*
Foluso Agboola, MBBS, MPH Director, Evidence Synthesis Institute for Clinical and Economic Review	
Steven D. Pearson, MD, MSc President Institute for Clinical and Economic Review	
David M. Rind, MD, MSc Chief Medical Officer Institute for Clinical and Economic Review	

None of the above authors disclosed any conflicts of interest.

DATE OF PUBLICATION: November 30, 2020

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 http://www.icer-review.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 http://www.icer-review.org/about/support/.

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-review.org/programs/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: **https://icer-review.org/material/anemia-in-chronic-kidney-disease-stakeholder-list/.**

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.

Table of Contents

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
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 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 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.[14,15] The HIF-PH inhibitor roxadustat (AstraZeneca) is under review by the Food and Drug Administration (FDA) with an expected decision date in December 2020.

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,[16] 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 four key unpublished Phase III RCTs of roxadustat.[17-20] We performed a meta-analysis (MA) of all-cause mortality in the three placebo-controlled trials and found a borderline statistically significant increased risk of all-cause mortality with roxadustat (risk ratio [RR]: 1.15, 95% CI: 1.00 to 1.33). In the one trial comparing roxadustat with an ESA, there were no statistically significant differences in the risk of MACE (hazard ratio [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). [17]

In the DD-CKD population, we also identified four key unpublished Phase III RCTs comparing roxadustat with ESAs.[19-22] 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).[16] We used available data from all four trials to perform a MA of all-cause mortality and found no statistically significant difference (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 may increase the risk for mortality and 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, and 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.

There is currently insufficient evidence to compare roxadustat and ESAs. Roxadustat provides an oral option for treating anemia of 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 support that conclusion. Cost effectiveness will depend on the manufacturer's price.

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.[23,24] 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 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.[25-28]

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.[29,30] 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.[31] 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.[32]

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 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-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) with an expected decision date in December 2020. 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,[33] 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 nine references relating to two RCTs comparing roxadustat to darbepoetin alfa[17,34] and seven RCTs comparing roxadustat to placebo[18-20,35-38] 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.[17-20] All of the RCTs are currently unpublished, and data for these trials was obtained from a clinical trial report, conference presentation, investor presentation, a pre-approval Academy of Managed Care Pharmacy (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.[17] 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.[19,20] 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,[20,22,37,39-42] two RCTs in incident and stable DD-CKD,[19,20] and one RCT in incident DD-CKD[20,21] met our inclusion criteria. A detailed description of these RCTs is included in the Report Supplement.

Key Trials of Roxadustat in the DD-CKD Population

We identified four Phase III, multicenter RCTs of roxadustat in DD-CKD.[19-22] 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).[19-21] 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.[20,22] 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: 36%
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: 59% 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](#).
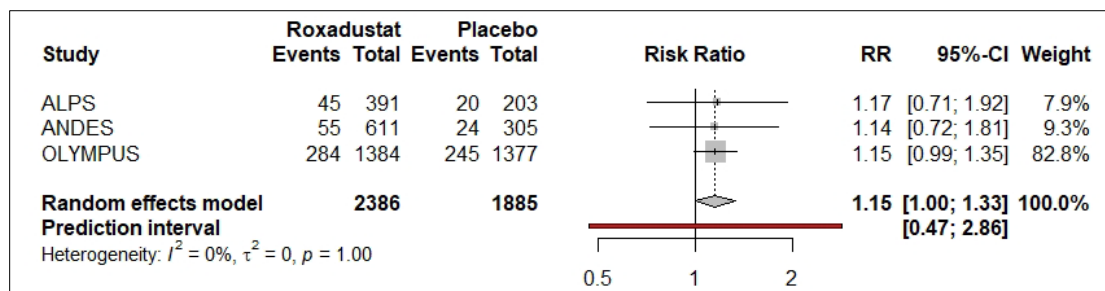
DI-CKD

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 10).

DOLOMITES RCT (roxadustat vs. darbepoetin alfa): At the time of this report, adjudicated cardiovascular events were reported in a non-confirmatory analysis.[17] There were no significant differences in the risk of MACE (hazard ratio [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) in the first 52 weeks.[16] However, the number of deaths in the individual RCTs exceeds that of the pooled analyses. As such, we performed a meta-analysis (MA) of all-cause mortality reported for ALPS, ANDES, and OLYMPUS.[20] As seen in Figure 3.1, the MA 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).

Figure 3.1. MA of All-Cause Mortality for ALPS, ANDES, and OLYMPUS

Study	Roxadustat Events	Total	Placebo Events	Total	Risk Ratio	RR	95%-CI	Weight
ALPS	45	391	20	203		1.17	[0.71; 1.92]	7.9%
ANDES	55	611	24	305		1.14	[0.72; 1.81]	9.3%
OLYMPUS	284	1384	245	1377		1.15	[0.99; 1.35]	82.8%
Random effects model		2386		1885		1.15	[1.00; 1.33]	100.0%
Prediction interval							[0.47; 2.86]	
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 1.00$								

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

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 in a pooled analysis of ALPS, ANDES, and OLYMPUS. Results for SF-36 are presented here, where higher scores indicate better quality of life. Results for the remaining assessments from the pooled analysis 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.[17] However, this difference did not exceed the MCID of 3 to 5 points.[43] 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).[17]

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.[44] However, MCIDs of 3 to 5 points were not reached in SF-36 PF or VT sub-scores in the pooled analysis.[43] Further, we performed MAs of these outcomes averaged over weeks 12 to 28 reported for ALPS and OLYMPUS.[18,19] The MAs found no significant differences in SF-36 PF sub-score (mean difference [MD]: 0.56; 95% CI: -0.25 to 1.37) or SF-36 VT sub-score (MD: 0.60; 95% CI: -3.07 to 4.26) 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 unclear if the differences reported for the pooled analysis would also lack statistical significance at later timepoints.

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.[16]

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).[17]

ALPS, ANDES, and OLYMPUS RCTs (roxadustat vs. placebo): We performed a MA 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.
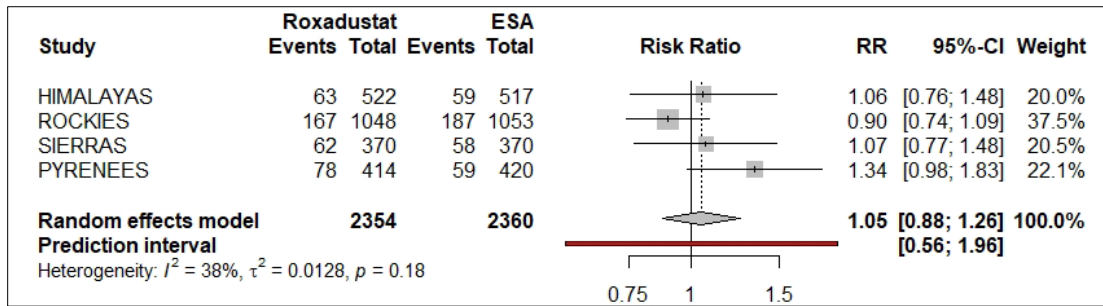
DD-CKD

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 25). 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.[16] However, the risk of MACE+ was reduced with roxadustat compared to epoetin alfa (HR: 0.85; 95% CI: 0.74 to 0.98).[16] 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).[20] Thus, we performed a MA of all-cause mortality reported for all four key RCTs (HIMALAYAS, PYRENEES, ROCKIES, and SIERRAS). As seen in Figure 3.2, the MA 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. MA of All-Cause Mortality in HIMALAYAS, PYRENEES, ROCKIES, and SIERRAS

95% CI: 95% confidence interval, ESA: erythropoiesis-stimulating agent, I²: I-squared, RR: risk ratio, τ²: 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 score (LSM difference: 0.52; 95% CI: -0.21, 1.25) averaged over weeks 12 to 28 with roxadustat compared to ESAs.[45] Notably, a MCID of 3 to 5 points was not reached in these assessments.[43]

Rescue Therapy

In PYRENEES, there was no significant difference in the risk of rescue therapy at end of treatment (up to week 104) with roxadustat compared to ESAs (HR: 0.98; 95% CI: 0.66 to 1.46).[22] Similar results for rescue therapy were reported for ROCKIES in the first 52 weeks (HR: 0.83; 95% CI: 0.64 to 1.07).[20]

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).[16]

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 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).[20,46]

Anemia

We performed a MA 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.[47] 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 treatment-emergent adverse events (TEAEs) were of mild-to-moderate severity (see Evidence Table 13).[17] 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 13).[20] The most commonly reported TEAEs included kidney failure, decrease in eGFR, nausea, hyperkalemia, and hypertension.[20] We conducted MAs of any TEAE and serious TEAEs for ALPS and ANDES and a MA of discontinuation due to adverse events for ALPS and OLYMPUS. There were no significant differences in the risk of any TEAE or serious TEAE with roxadustat compared to placebo (see Table D11, Figure D15, and Figure D16 in the Report Supplement); however, 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 D17 in the Report Supplement). Serious adverse events reported included all-cause mortality and cardiovascular events, which are presented above. Results for adverse events reported in the key RCTs should be interpreted with caution as the timepoints in which they were reported are unclear (timeframe between one and four years of treatment).

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 28).[20] We conducted MAs of any TEAE and serious TEAEs for HIMALAYAS, PYRENEES, and SIERRAS and a MA 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. Results for adverse events reported in the key RCTs should be interpreted with caution as the timepoints in which they were reported are unclear (timeframe between one and four years of treatment).

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 16). We describe the subgroups of patients defined by iron and inflammation states and those with incident DD-CKD below.

DI-CKD

ALPS, ANDES, and OLYMPUS RCTs (roxadustat vs. placebo): We identified eight references for subgroup analyses of the key RCTs and pooled analysis.[16,20,44,48-52] 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 33, and Evidence Table 36). 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 33 and Evidence Table 36). Qualitatively, there were no subgroup effects based on iron or inflammation states.

DD-CKD

We identified three references for subgroup analyses of HIMALAYAS, ROCKIES, SIERRAS and a pooled analysis of these RCTs.[20,21,53] 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 23 and Evidence Table 34). 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.[39,40]

Incident Dialysis Subgroup

We identified one reference for a subgroup analysis of incident DD-CKD patients.[54] 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 38). 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.[16]

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.[33] We believe results from PYRENEES should be included in the pooled safety and efficacy analyses.

Given changes to recommended Hb target 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.

3.3. Summary and Comment

An explanation of the ICER Evidence Rating Matrix (Figure 3.3) is provided in the Report Supplement.

Figure 3.3. ICER Evidence Rating Matrix

Comparative Clinical Effectiveness

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

The key trials (ALPS, ANDES, and OLYMPUS) have not been published, 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.

Available data found an increase in all-cause mortality with roxadustat of borderline statistical significance (HR: 1.15; 95% CI: 1.00 to 1.33). However, 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 no increase in deaths to five additional deaths per 100 patients (timeframe between one and four 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
DI-CKD		
Roxadustat	ESAs (i.e., darbepoetin alfa)	*Insufficient (I)*
	Usual care (estimated by the placebo arms of clinical trials)	*Promising but inconclusive (P/I)*
DD-CKD		
Roxadustat	ESAs (i.e., epoetin alfa and darbepoetin alfa)	*Insufficient (I)*

DI: dialysis-independent, DD: dialysis-dependent, ESA: erythropoiesis-stimulating agent
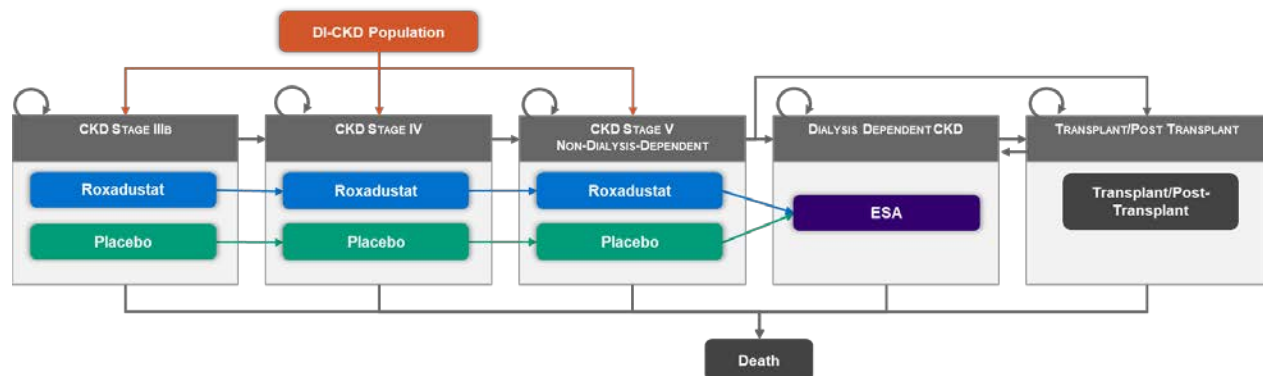
4. Long-Term Cost-Effectiveness

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, red blood cell 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

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

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 MA showed similar efficacy across ESAs.[55]
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, MA: meta-analysis

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 stage 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.[56] 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.[56] 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[57]
Baseline DI-CKD Stage IV/V without Anemia	0.72	Nguyen 2018; EQ-5D[57]
Baseline DD-CKD ESRD without Anemia	0.609 (0.566, 0.652)	Manns 2003; EQ-5D[58]
Utility Increase Post Transplant	0.13	Laupacis 1996; TTO[59]
Utility Loss per 1 g/dl Decrease in Hb (Reference Hb ≥13 g/dL)	0.0114	Finkelstein 2009;[56] SF-36 & mapping function from Ara 2008[60] as cited in Yarnoff 2016[61]

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).[16,62] 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 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.[16] 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)	16
Stroke	2.3%	2.6%	0.90 (0.60, 1.34)	16
Unstable Angina	0.9%	1.1%	0.82 (0.44, 1.52)	16
CHF Hospitalization	6.2%	8.6%	0.72 (0.58, 0.91)	16,63

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 occurs 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, red blood cell 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 red blood cell 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]).[64]

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, red blood cell infusions, or MACE+. As there were negligible differences in quality-adjusted life years (QALYs) and equal value of 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 (-$8,220) due to the lower assumed cost of roxadustat versus ESAs and lower use of IV iron.

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	$374,478	$430,000	5.38	7.64	5.38
Roxadustat	$46,000	$1,021	$283	$374,478	$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 red blood cell transfusions, and point estimates for reduction in MACE+.

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	$799,877	$833,711	3.84	6.35	3.84
Roxadustat	$30,000	$4,390	$285	$768,890	$803,673	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≥ 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 red blood cell transfusions, and point estimates for reduction in MACE+. 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	$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.
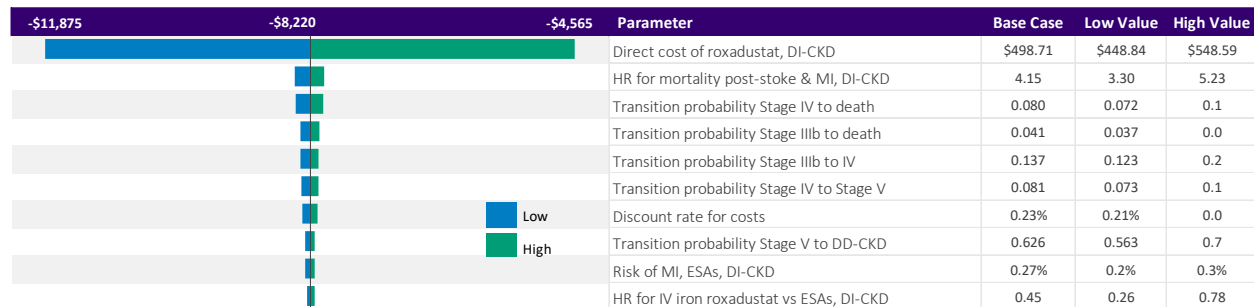
†Includes adverse events, MACE+, and cost of Medicare bundled payment.

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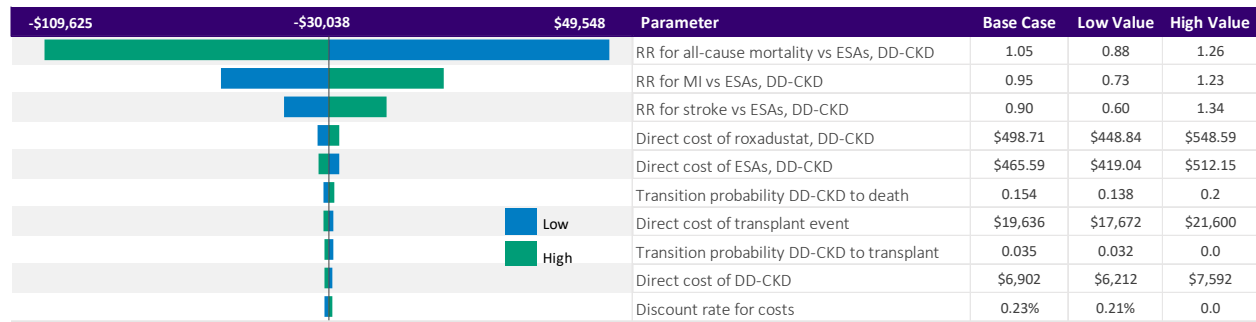
Sensitivity Analyses

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

			Parameter	Base Case	Low Value	High Value
-$11,875	-$8,220	-$4,565	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
			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
		Low	Discount rate for costs	0.23%	0.21%	0.0
		High	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%
			HR for IV iron roxadustat vs ESAs, DI-CKD	0.45	0.26	0.78

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
Transition probability DD-CKD to transplant	0.035	0.032	0.0
Direct cost of DD-CKD	$6,902	$6,212	$7,592
Discount rate for costs	0.23%	0.21%	0.0

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, the incremental cost per QALY for roxadustat versus ESAs exceeded the $150,000 per QALY threshold.

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	-$30,000	-$41,000	$1,600
Incremental QALYs	-0.09	-0.09	0.01
Roxadustat vs. ESAs, Medicare Perspective			
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 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 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.

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. However, the cost per QALY for roxadustat in this scenario was $349,000, exceeding the threshold of $150,000 per QALY using a placeholder price of $6,500 per year.

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.

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. A scenario was conducted to remove MACE+ from the analysis due to uncertainty in the true relative effect. In this scenario, the cost per QALY exceeded $150,000 from a commercial perspective and was near $2 million per QALY from the Medicare perspective, but these high incremental cost-effectiveness ratios are the result of small QALY gains and the placeholder net price for roxadustat.

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. 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

Potential Other Benefit or Contextual Consideration	Relevant Information
	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 the DD-CKD population). See 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 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

6. Health Benefit Price Benchmarks

ICER does not provide health benefit price benchmarks as part of the draft Evidence Report because results may change with revision following receipt of public comments. We therefore caution readers against assuming that the values provided in the Threshold Prices section of this report will match the health benefit price benchmarks that will be presented in the next version of this report.

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 treatment with roxadustat compared with ESAs for anemia in patients with DI-CKD and in patients with DD-CKD. 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[65,66]
    - 42.9% are stage III; 2.5% are stage IV; 0.9% are stage V[66]
    - 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 taking ESAs and N=38,232 DD-CKD patients taking ESAs and therefore eligible to 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.

References

1. Hsu CY. Epidemiology of anemia associated with chronic renal insufficiency. *Current opinion in nephrology and hypertension.* 2002;11(3):337-341.
2. Hsu CY, McCulloch CE, Curhan GC. Epidemiology of anemia associated with chronic renal insufficiency among adults in the United States: results from the Third National Health and Nutrition Examination Survey. *Journal of the American Society of Nephrology : JASN.* 2002;13(2):504-510.
3. Astor BC, Muntner P, Levin A, Eustace JA, Coresh J. Association of kidney function with anemia: the Third National Health and Nutrition Examination Survey (1988-1994). *Archives of internal medicine.* 2002;162(12):1401-1408.
4. Stauffer ME, Fan T. Prevalence of anemia in chronic kidney disease in the United States. *PloS one.* 2014;9(1):e84943-e84943.
5. Smith RE, Jr. The clinical and economic burden of anemia. *The American journal of managed care.* 2010;16 Suppl Issues:S59-66.
6. Kidney Disease Outcomes Quality Initiative (KDOQI). KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 2006;47(5 Suppl 3):S11-145.
7. Eschbach JW. Erythropoietin 1991--an overview. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 1991;18(4 Suppl 1):3-9.
8. Eschbach JW, Egrie JC, Downing MR, Browne JK, Adamson JW. Correction of the anemia of end-stage renal disease with recombinant human erythropoietin. Results of a combined phase I and II clinical trial. *N Engl J Med.* 1987;316(2):73-78.
9. KDOQI Clinical Practice Guideline and Clinical Practice Recommendations for anemia in chronic kidney disease: 2007 update of hemoglobin target. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 2007;50(3):471-530.
10. Palmer SC, Navaneethan SD, Craig JC, et al. Meta-analysis: erythropoiesis-stimulating agents in patients with chronic kidney disease. *Annals of internal medicine.* 2010;153(1):23-33.
11. Bohlius J, Schmidlin K, Brillant C, et al. Erythropoietin or Darbepoetin for patients with cancer--meta-analysis based on individual patient data. *The Cochrane database of systematic reviews.* 2009;2009(3):Cd007303.
12. Phrommintikul A, Haas SJ, Elsik M, Krum H. Mortality and target haemoglobin concentrations in anaemic patients with chronic kidney disease treated with erythropoietin: a meta-analysis. *Lancet (London, England).* 2007;369(9559):381-388.
13. Strippoli GF, Navaneethan SD, Craig JC. Haemoglobin and haematocrit targets for the anaemia of chronic kidney disease. *The Cochrane database of systematic reviews.* 2006(4):Cd003967.
14. Holdstock L, Meadowcroft AM, Maier R, et al. Four-Week Studies of Oral Hypoxia-Inducible Factor-Prolyl Hydroxylase Inhibitor GSK1278863 for Treatment of Anemia. *Journal of the American Society of Nephrology : JASN.* 2016;27(4):1234-1244.
15. Provenzano R, Besarab A, Wright S, et al. Roxadustat (FG-4592) Versus Epoetin Alfa for Anemia in Patients Receiving Maintenance Hemodialysis: A Phase 2, Randomized, 6- to 19-Week, Open-Label, Active-Comparator, Dose-Ranging, Safety and Exploratory Efficacy Study. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 2016;67(6):912-924.

16. Provenzano R, Fishbane S, Wei L-J, et al. Pooled Efficacy and CV Safety Results of Roxadustat in the Treatment of Anemia in Chronic Kidney Disease (CKD) Patients On and Not on Dialysis. https://fibrogen.gcs-web.com/static-files/c456ad75-05bd-4b48-915c-84c3743dc3fb. Published 2019. Accessed.

17. Barratt J. Roxadustat for the Treatment of Anaemia in Chronic Kidney Disease Patients Not on Dialysis: A Phase 3, Randomised, Open-Label, Active-Controlled Study. ERA-EDTA; June 6-9, 2020, 2020.

18. Astellas I. A Phase 3, Randomized, Double-Blind, Placebo Controlled Study of the Efficacy and Safety of Roxadustat for the Treatment of Anemia in Chronic Kidney Disease Patients not on Dialysis (ISN 1517-CL-0608). https://astellasclinicalstudyresults.com/study.aspx?ID=363. Published 2019. Accessed October 29, 2020.

19. AstraZeneca. Investor science call: American Society of Nephrology Kidney Week 2019. https://www.astrazeneca.com/content/dam/az/Investor_Relations/events/AZN%20Investor%20science%20conference%20call%20ASN%202019%20Presentation.pdf. Published 2019. Accessed.

20. AstraZeneca. *Roxadustat: AMCP Unapproved Product Dossier.* 2020.

21. Provenzano R, Shutov E, Liubov E, et al. HIMALAYAS: A Phase 3, Randomized, Open-Label, Active-Controlled Study of the Efficacy and Safety of Roxadustat in the Treatment of Anemia in Incident-Dialysis Patients. fibrogen.com. http://investor.fibrogen.com/static-files/8720f26b-e86f-4770-bfb9-0fb1e45da3a1. Published 2019. Accessed.

22. Astellas I. A Phase 3, Randomized, Open-Label, Active-Controlled Study to Evaluate the Efficacy and Safety of Roxadustat in the Maintenance Treatment of Anemia in End Stage Renal Disease Subjects on Stable Dialysis. https://astellasclinicalstudyresults.com/study.aspx?ID=364. Published 2019. Accessed.

23. World Health Organization. *Worldwide prevalence of anaemia 1993-2005 : WHO global database on anaemia.* Geneva: World Health Organization; 2008 2008. 9789241596657.

24. Chapter 1: Diagnosis and evaluation of anemia in CKD. *Kidney Int Suppl (2011).* 2012;2(4):288-291.

25. Khan S, Pereira BJ. Hematocrit level associated mortality in hemodialysis patients, by Ma JZ, Ebben J, Xia H, Collins AJ. J Am Soc Nephrol 10:610-619, 1999. *Seminars in dialysis.* 2000;13(2):112-113.

26. Xia H, Ebben J, Ma JZ, Collins AJ. Hematocrit levels and hospitalization risks in hemodialysis patients. *Journal of the American Society of Nephrology : JASN.* 1999;10(6):1309-1316.

27. Collins AJ, Li S, St Peter W, et al. Death, hospitalization, and economic associations among incident hemodialysis patients with hematocrit values of 36 to 39%. *Journal of the American Society of Nephrology : JASN.* 2001;12(11):2465-2473.

28. Collins AJ, Ma JZ, Ebben J. Impact of hematocrit on morbidity and mortality. *Seminars in nephrology.* 2000;20(4):345-349.

29. Levey AS, Titan SM, Powe NR, Coresh J, Inker LA. Kidney Disease, Race, and GFR Estimation. *Clinical Journal of the American Society of Nephrology.* 2020:CJN.12791019.

30. Stevens LA, Coresh J, Greene T, Levey AS. Assessing Kidney Function — Measured and Estimated Glomerular Filtration Rate. *New England Journal of Medicine.* 2006;354(23):2473-2483.

31. National Kidney Foundation. Chronic Kidney Disease (CKD) Symptoms and causes. National Kidney Foundation. https://www.kidney.org/atoz/content/about-chronic-kidney-disease. Published 2020. Accessed 11/25/20, 2020.

32.   Gregorio T. Obrador M, MPH. Epidemiology of chronic kidney disease. 2018. https://www.uptodate.com/contents/epidemiology-of-chronic-kidney-disease. Published June 4, 2018. Accessed 7/17/20.

33.   Palmer SC, Saglimbene V, Mavridis D, et al. Erythropoiesis-stimulating agents for anaemia in adults with chronic kidney disease: a network meta-analysis. *The Cochrane database of systematic reviews.* 2014;2014(12):Cd010590.

34.   Akizawa T, Iwasaki M, Otsuka T, Yamaguchi Y, Reusch M. A Phase 3, Multicenter, Randomized, Open-Label, Active Comparator Conversion Study of Roxadustat in Non-Dialysis-Dependent (NDD) Patients with Anemia in CKD. ASN 2020; 22-25 October, 2020, 2020.

35.   Chen N, Hao C, Peng X, et al. Roxadustat for Anemia in Patients with Kidney Disease Not Receiving Dialysis. *New England Journal of Medicine.* 2019;381(11):1001-1010.

36.   Besarab A, Provenzano R, Hertel J, et al. Randomized placebo-controlled dose-ranging and pharmacodynamics study of roxadustat (FG-4592) to treat anemia in nondialysis-dependent chronic kidney disease (NDD-CKD) patients. *Nephrology Dialysis Transplantation.* 2015;30(10):1665-1673.

37.   Chen N, Qian J, Chen J, et al. Phase 2 studies of oral hypoxia-inducible factor prolyl hydroxylase inhibitor FG-4592 for treatment of anemia in China. *Nephrology Dialysis Transplantation.* 2017;32(8):1373-1386.

38.   Akizawa T, Iwasaki M, Otsuka T, Reusch M, Misumi T. Roxadustat Treatment of Chronic Kidney Disease-Associated Anemia in Japanese Patients Not on Dialysis: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Trial. *Advances in Therapy.* 2019;36(6):1438-1454.

39.   Chen N, Hao C, Liu B-C, et al. Roxadustat Treatment for Anemia in Patients Undergoing Long-Term Dialysis. *New England Journal of Medicine.* 2019;381(11):1011-1022.

40.   Akizawa T, Iwasaki M, Yamaguchi Y, Majikawa Y, Reusch M. Phase 3, Randomized, Double-Blind, Active-Comparator (Darbepoetin Alfa) Study of Oral Roxadustat in CKD Patients with Anemia on Hemodialysis in Japan. *Journal of the American Society of Nephrology.* 2020;31(7):1628-1639.

41.   Provenzano R, Besarab A, Wright S, et al. Roxadustat (FG-4592) Versus Epoetin Alfa for Anemia in Patients Receiving Maintenance Hemodialysis: A Phase 2, Randomized, 6- to 19-Week, Open-Label, Active-Comparator, Dose-Ranging, Safety and Exploratory Efficacy Study. *American Journal of Kidney Diseases.* 2016;67(6):912-924.

42.   Astellas I. A Japanese, Phase 2, Multicenter, Randomized, 4-arm Parallel, Double-blind (Arms 1-3), Open-label (Arm 4), Active-comparator (Darbepoetin Alfa) Study of Intermittent Oral Dosing of ASP1517 in Hemodialysis-dependent Chronic Kidney Disease Patients with Anemia. https://astellasclinicalstudyresults.com/study.aspx?ID=355. Published 2018. Accessed.

43.   Leaf DE, Goldfarb DS. Interpretation and review of health-related quality of life data in CKD patients receiving treatment for anemia. *Kidney international.* 2009;75(1):15-24.

44.   Coyne DW, Manllo-Karim R, Pergola PE, et al. Health-Related Quality of Life in Roxadustat-Treated Patients With Anemia and Non-Dialysis-Dependent Chronic Kidney Disease. ASN 2020; 22-25 October, 2020, 2020.

45.   clinicaltrials.gov. Safety and Efficacy Study of Roxadustat to Treat Anemia in Patients With Chronic Kidney Disease (CKD), Not on Dialysis. https://clinicaltrials.gov/ct2/show/NCT02174627. Published 2019. Updated December 16, 2019. Accessed.

46.   Astellas I. A Phase 3, Randomized, Open-Label, Active-Controlled Study to Evaluate the Efficacy and Safety of Roxadustat in the Maintenance Treatment of Anemia in End Stage Renal Disease Subjects on Stable Dialysis. https://ascrstudypdfs.blob.core.windows.net/ascrstudypdfs/1517-cl-0613-clrrs-02-disc01-en-final-02.pdf. Published 2019. Accessed October 14, 2020.

47. The Pharmaceuticals and Medical Devices Agency. Report on the Deliberation Results. https://www.pmda.go.jp/files/000234811.pdf. Published 2019. Accessed.

48. Provenzano R, Fishbane, S., Coyne, D., Pollock, C., Pola, M., Chou, W., Saikali, K., YU, KHP. Roxadustat Treatment of Anemia in Non-Dialysis Dependent Chronic Kidney Disease is Not Influenced by Iron Status. NKF 2020; 2020.

49. Coyne DW, El-Shahawy MA, Pecoits-Filho R, et al. Subgroup Analyses of Efficacy of Roxadustat for Treatment of Anemia in Patients With Non-Dialysis-Dependent Chronic Kidney Disease. ASN 2020; 22-25 October 2020, 2020.

50. Pollock CA, Roger SD, Manllo-Karim R, et al. Roxadustat Increases Hemoglobin in Anemic Non-Dialysis-Dependent (NDD) Chronic Kidney Disease (CKD) Patients Independent of Inflammation. ASN 2020; 2020.

51. Provenzano R, Fishbane S, Coyne DW, et al. Roxadustat Treatment of Anemia in Non-Dialysis-Dependent Chronic Kidney Disease Is Not Influenced by Iron Status. ASN 2020; 22-25 October 2020, 2020.

52. Pecoits-Filho R, Chan TM, Hardy E, Yu KP, Fishbane S. Roxadustat Treatment Results in Consistent Improvements in Hemoglobin (Hb) Versus Placebo: An Analysis of 3 Multinational RCTs in Patients With Non-Dialysis-Dependent Chronic Kidney Disease (NDD-CKD). ASN 2020; 22-25 October 2020, 2020.

53. El-Shahawy MA, Roger SD, Manllo-Karim R, et al. Roxadustat Increases Hemoglobin in Anemic Dialysis-Dependent (DD) Chronic Kidney Disease (CKD) Patients Independent of Inflammation. ASN 2020; 22–25 October 2020, 2020.

54. Provenzano R, Kumar J, Fishbane S, et al. Subgroup Analyses of Efficacy of Roxadustat for Treatment of Anemia in Patients With Incident Dialysis–Dependent Chronic Kidney Disease. ASN 2020; 22-25 October, 2020, 2020.

55. Amato L, Addis A, Saulle R, Trotta F, Mitrova Z, Davoli M. Comparative efficacy and safety in ESA biosimilars vs. originators in adults with chronic kidney disease: a systematic review and meta-analysis. *J Nephrol.* 2018;31(3):321-332.

56. Finkelstein FO, Story K, Firanek C, et al. Health-related quality of life and hemoglobin levels in chronic kidney disease patients. *Clin J Am Soc Nephrol.* 2009;4(1):33-38.

57. Nguyen NTQ, Cockwell P, Maxwell AP, Griffin M, O'Brien T, O'Neill C. Chronic kidney disease, health-related quality of life and their associated economic burden among a nationally representative sample of community dwelling adults in England. *PLoS One.* 2018;13(11):e0207960.

58. Manns B, Johnson JA, Taub K, Mortis G, Ghali WA, Donaldson C. Quality of life in patients treated with hemodialysis or peritoneal dialysis: what are the important determinants? *Clin Nephrol.* 2003;60(5):341-351.

59. Laupacis A, Keown P, Pus N, et al. A study of the quality of life and cost-utility of renal transplantation. *Kidney international.* 1996;50(1):235-242.

60. Ara R, Brazier J. Deriving an algorithm to convert the eight mean SF-36 dimension scores into a mean EQ-5D preference-based score from published studies (where patient level data are not available). *Value Health.* 2008;11(7):1131-1143.

61. Yarnoff BO, Hoerger TJ, Simpson SA, et al. The Cost-Effectiveness of Anemia Treatment for Persons with Chronic Kidney Disease. *PLoS One.* 2016;11(7):e0157323.

62. Barratt J, Andrić B, Tataradze A, et al. Roxadustat for the treatment of anaemia in chronic kidney disease patients not on dialysis: A phase 3, randomised, open-label, active-controlled study. *Nephrology Dialysis Transplantation.* 2020;35(Supplement_3).

63. Provenzano R, Szczech L, Zhong M, et al. Pooled Analyses of the Phase 3 Roxadustat Studies: Congestive Heart Failure Hospitalization Rates in Dialysis and Non-Dialysis Patients with Anemia Treated with Roxadustat vs. Comparators. ASN 2020; 22-25 October, 2020, 2020.
64. Amgen. Parsabiv® is reimbursed as a Transitional Drug Add-on Payment Adjustment (TDAPA) through 2020. https://www.parsabivhcp.com/reimbursement. Published 2020. Accessed November 9, 2020.
65. Centers for Disease Control and Prevention. https://www.cdc.gov/kidneydisease/pdf/2019_National-Chronic-Kidney-Disease-Fact-Sheet.pdf. Accessed 11/20/2020.
66. United States Renal Data System. https://adr.usrds.org/2020/chronic-kidney-disease/1-ckd-in-the-general-population. Accessed 11/20/2020.