Treatments for Anemia in Chronic Kidney Disease: Effectiveness and Value

Public Meeting — February 11, 2021

ICER
INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

Why Are We Here Today?

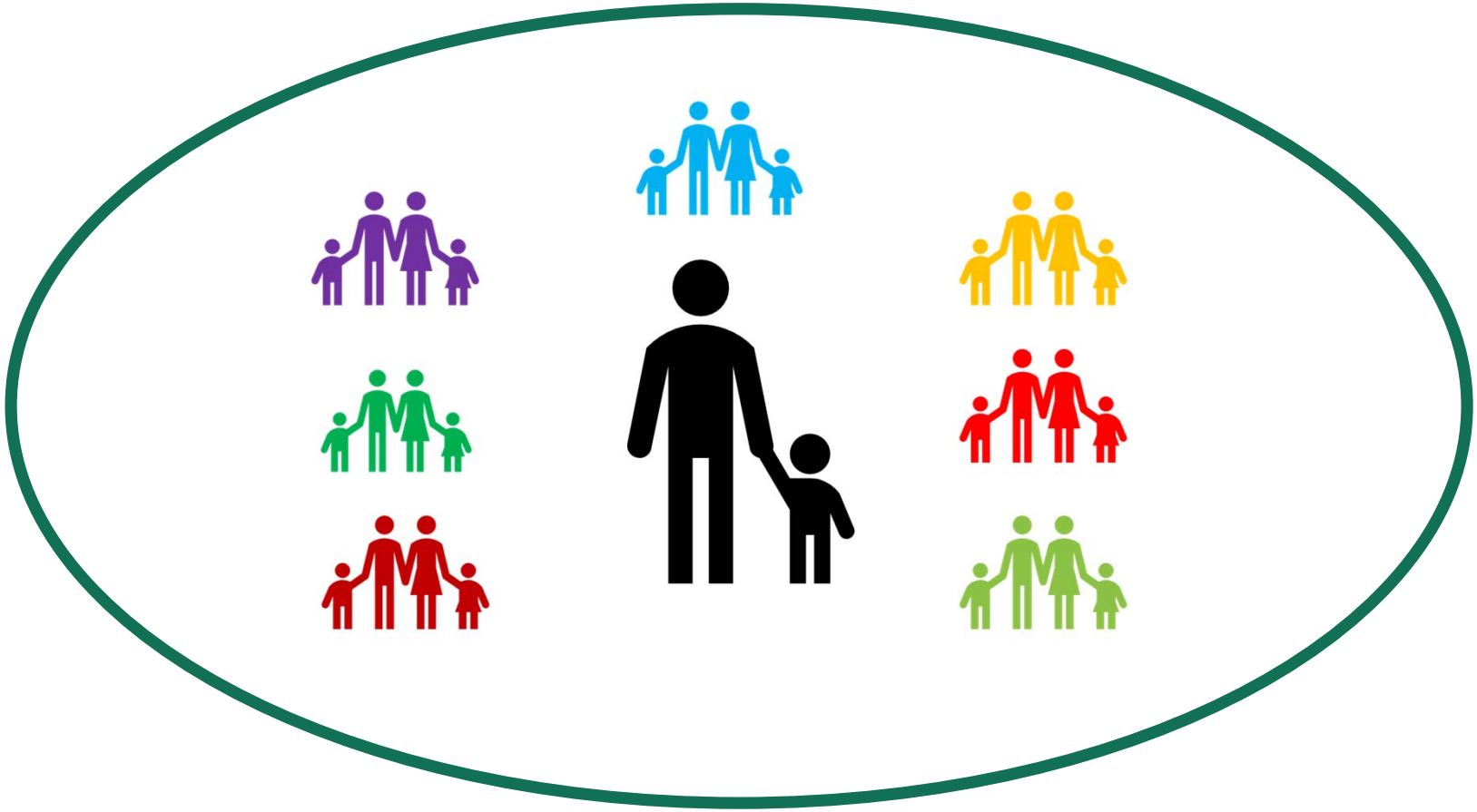
Managing my anemia has probably been the biggest challenge for me. It impacted my energy levels to an unbelievable degree, and as a naturally social and busy person, that was very hard for me mentally and emotionally. Finding a treatment that worked was quite a journey. It required constant adjustments in medications until I found a balance that made me feel good day-to-day. I'm lucky to have found something that worked – I know many other people with CKD are still trying to find that balance.

Patient with CKD

Why Are We Here Today?

- What happens the day these treatments are approved by the FDA?
- Patients can have difficulty accessing drugs
  - Coverage eligibility
  - Costs (out-of-pocket and insurance premiums)
- What happens to patients and others in the health care “system”?

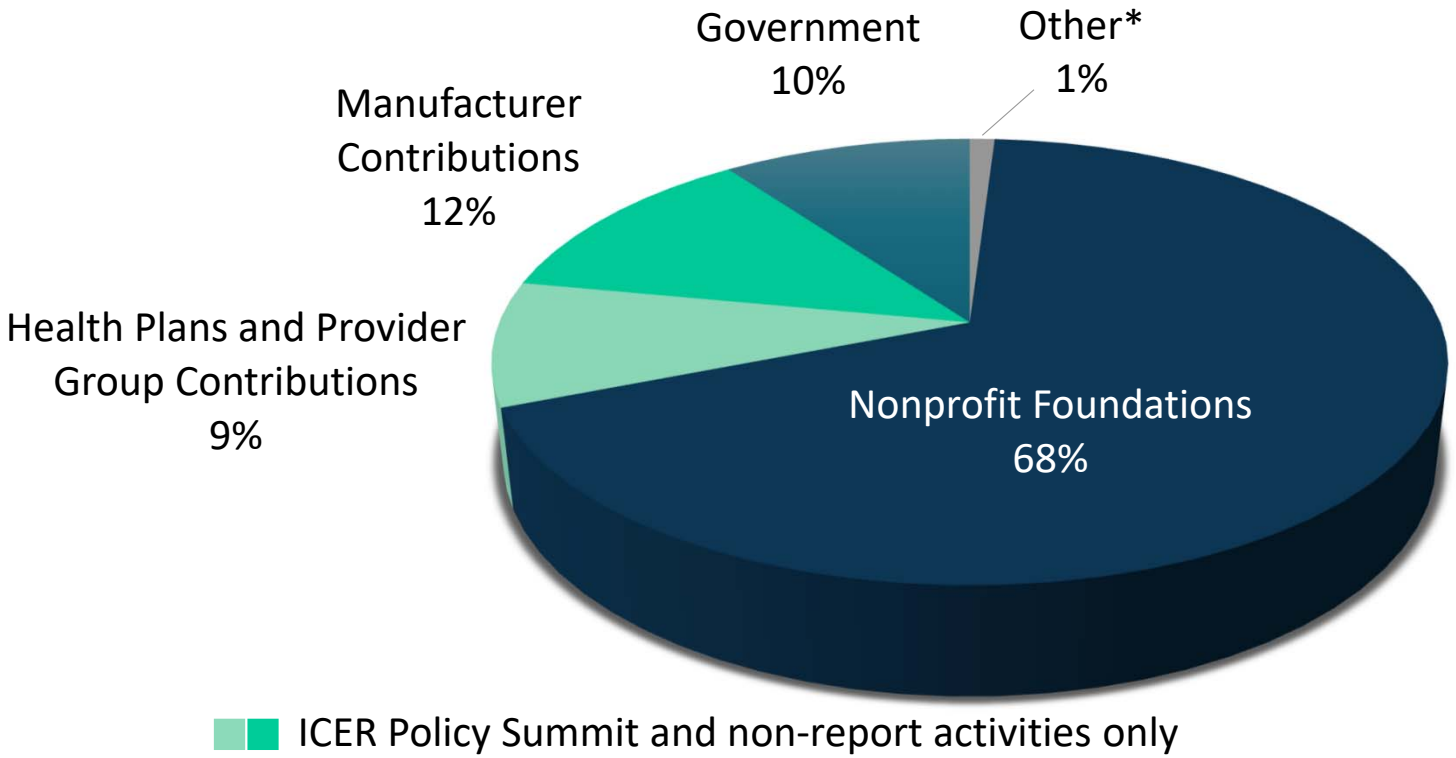
When There Isn’t Enough Money For Health Insurance



Organizational Overview

- The California Technology Assessment Forum (CTAF)
- The Institute for Clinical and Economic Review (ICER)

2021 Funding



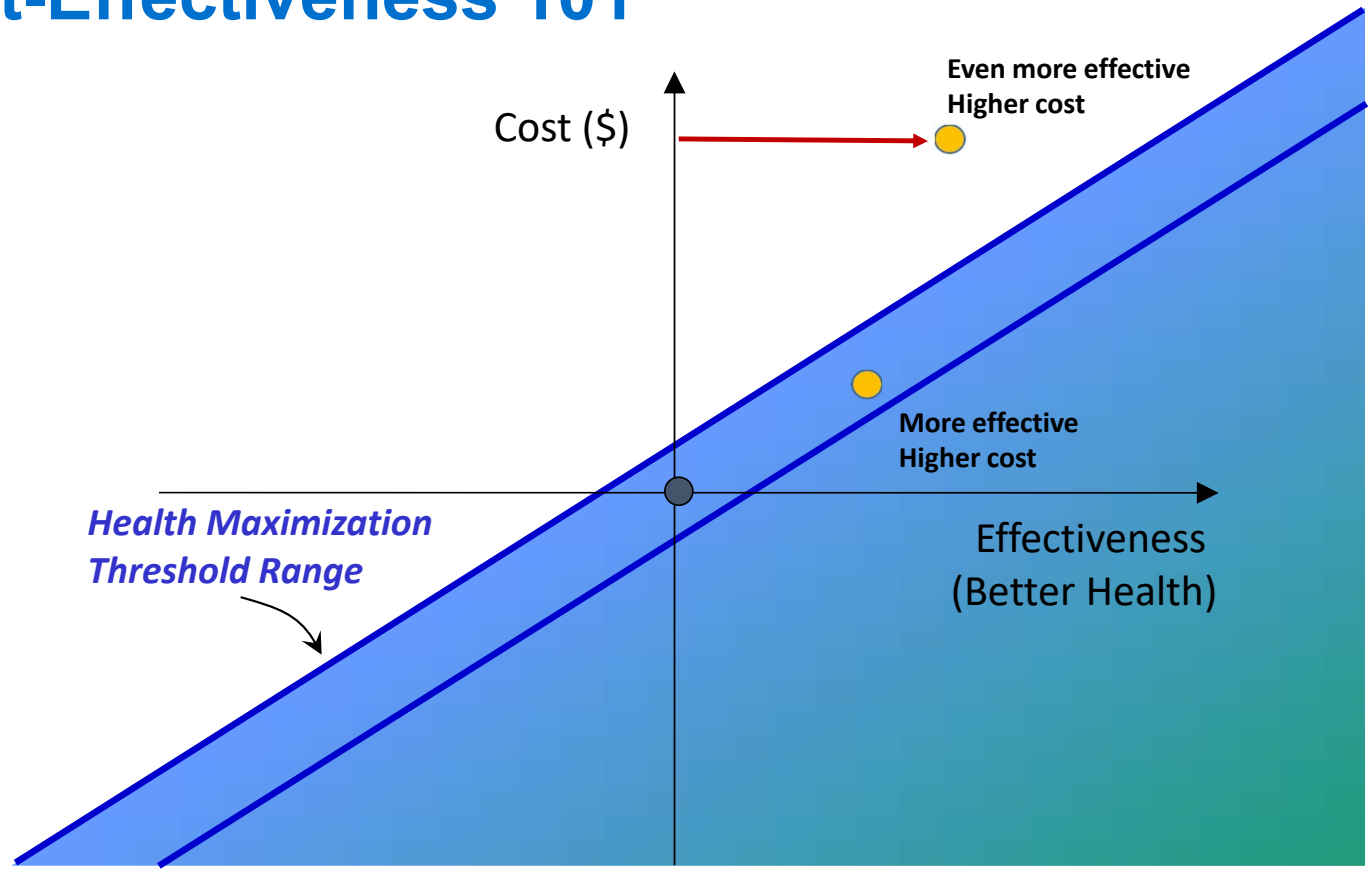
*Individual/matching contributions and speech stipends

How Was the ICER Report Developed?

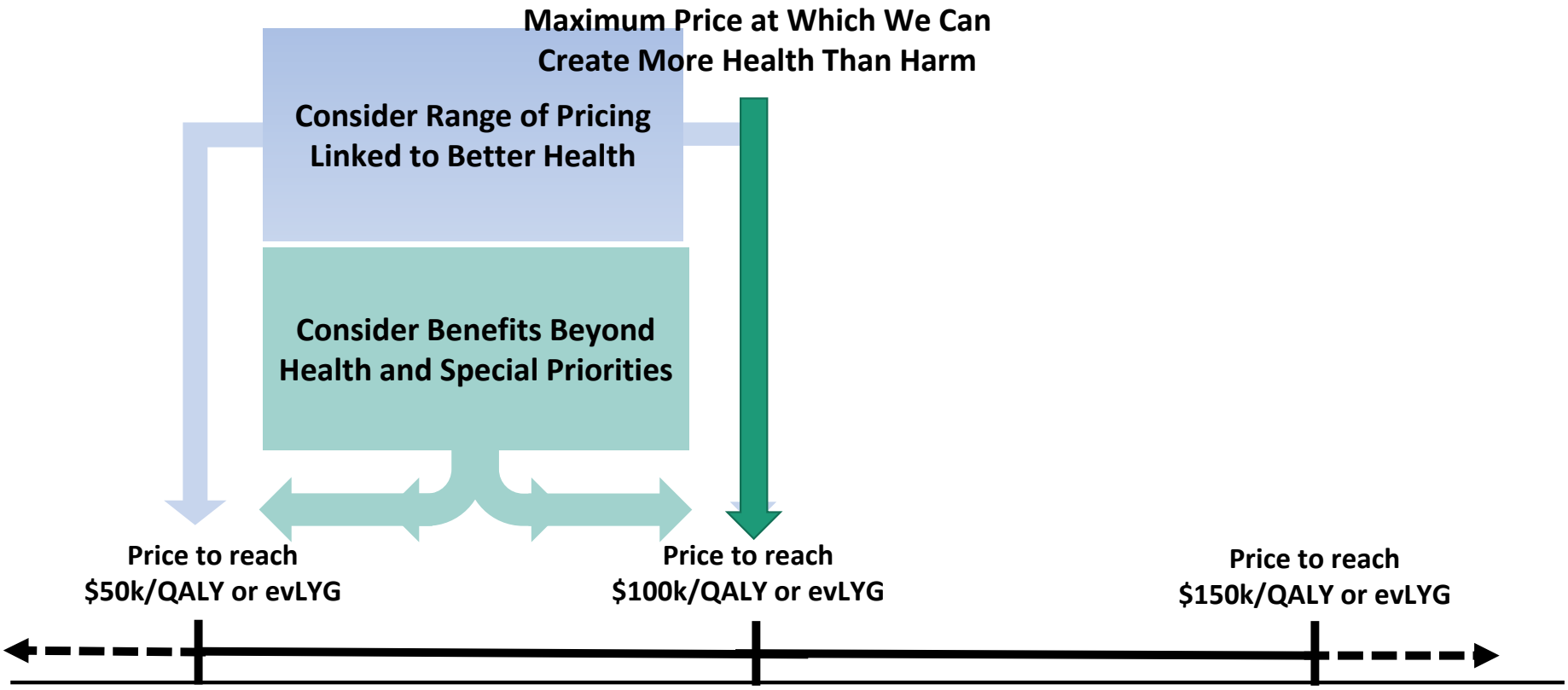
- Scoping with guidance from patient groups, clinical experts, manufacturers, and other stakeholders
- Internal ICER staff evidence analysis
- University of Washington cost-effectiveness modeling
- Public comment and revision
- Expert reviewers
  - Jeffrey S. Berns, MD, Professor of Medicine; Associate Chief, Renal Electrolyte and Hypertension, University of Pennsylvania
  - Pinelopi Kapitsinou, MD, Associate Professor of Medicine, Division of Nephrology and Hypertension, Northwestern University, Feinberg School of Medicine
- How is the evidence report structured to support CTAF voting and policy discussion?

Value Assessment Framework: Long-Term Value for Money

Cost-Effectiveness 101



Integrating Elements of Long-Term Value for Money



Agenda (All Times PT)

9:00	Meeting Convened and Opening Remarks
9:15	Presentation of the Evidence
10:25	Break
10:35	Manufacturer Public Comments and Discussion
10:55	Public Comments and Discussion
11:05	Lunch
11:55	CTAF Vote on Clinical Effectiveness and Value
12:35	Policy Roundtable
1:35	Reflections from CTAF
2:00	Meeting Adjourned

Presentation of the Clinical Evidence

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Key Collaborators

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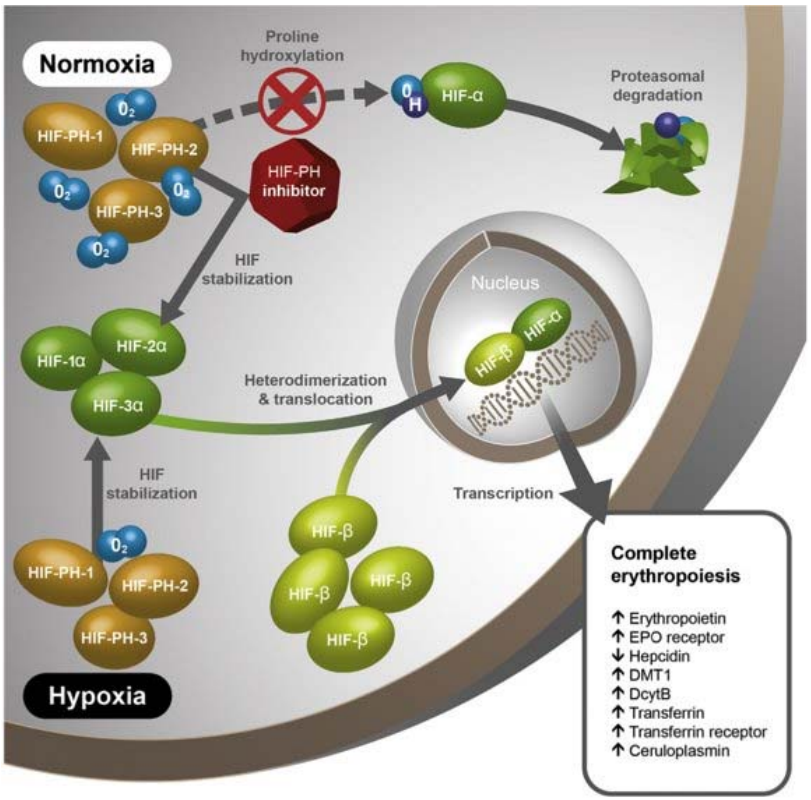
Disclosures:

- We have no conflicts of interest relevant to this report

Background

- Anemia is common in patients with chronic kidney disease (CKD) and becomes more prevalent as CKD progresses from DI-CKD to DD-CKD
- Fatigue affects living experience and QoL of patients with CKD
- Pre-ESA era: Blood transfusion and transplant
- Post-ESA approval (1990): Rapid and widespread uptake of ESA use in patients with CKD
  - Association between anemia and higher mortality in uncontrolled studies
- Subsequent RCTs showed correction of anemia and maintenance of Hb to near normal levels with ESAs **increased mortality and CV events without consistently improving QoL**

Background



- Hypoxia-inducible factor prolyl hydroxylase (HIF-PH) inhibitors have emerged as orally-administered agents
  - HIF-PH inhibitors induce lower, but more consistent, erythropoietin levels compared to ESAs
  - Hypothesized that they could cause fewer adverse CV events than ESAs

Insights from Discussions with Patients

- Patients place high value on autonomy and ability to maintain ADLs
- Fatigue: “It was something that I really had to manage because it really affected my energy level…”
- Some patients feel better after anemia treatment and some do not
- Desire for more choices related to anemia management
  - Experience side effects with ESAs
  - Do not tolerate ESAs
  - Not responsive or unable to achieve target Hb levels with ESAs
  - ESAs are contraindicated

Insights from Discussions with Patients

- ESA choice is dependent on factors that are typically not patient-related
  - Patients prefer longer acting ESA/less frequent injections
  - Specific ESA products are used by different dialysis providers
  - ESA availability varies for inpatient vs. outpatient care – formulary
  - Different ESAs are used differentially for DI-CKD or DD-CKD based on market agreements
- Supporting innovation and new treatment options
- Concerns that Medicare bundled payment system could stifle innovation

Scope of Review

- Population: Adult patients with anemia and CKD
  - Patients with DI-CKD: Stages of CKD: III, IV, and V
  - Patients with DD-CKD: Patients newly initiated on dialysis (ID-CKD)
- Subgroups:
  - ESA-hyporesponsiveness – inflammation state
  - CVD
  - Cancer
- We performed a meta-analysis for roxadustat

Outcomes

- Patient-important outcomes
  - All-cause mortality
  - CV mortality
  - Stroke
  - MI
  - Unstable angina
  - Heart failure
  - Hospitalization
  - Blood transfusion
  - Rescue therapy
  - ESKD
  - Health-related QoL
  - Improvement in symptoms or function (e.g., fatigue)
  - Adverse events
- Other outcomes
  - Anemia (as assessed by Hb and/or hematocrit)
  - Measures of iron storage and availability
  - Measures of inflammation
  - Lipid levels
  - CKD progression (as assessed by eGFR)

Clinical Evidence

Evidence map of key trials

- DI-CKD
  - Roxadustat vs. ESA (darbepoetin alfa)
    - 1 RCT
- DI-CKD
  - Roxadustat vs. Placebo
    - 3 RCTs
- DD-CKD (roxadustat vs. ESA)
  - Roxadustat vs. epoetin alfa
    - 1 Incident DD-CKD
    - 2 Incident and stable DD-CKD
  - Roxadustat vs. darbepoetin alfa and epoetin alfa
    - 1 RCT PYRENEES (stable DD-CKD)

Outcomes	DI-CKD Roxadustat vs. ESA (DOLOMITES)
CV Safety	
MACE*	HR (95% CI): 0.81 (0.52, 1.25) during safety emergent period
MACE+[†]	HR (95% CI): 0.90 (0.61, 1.32) during safety emergent period
All-Cause Mortality	HR (95% CI): 0.83 (0.50, 1.38) up to 1-2 years of treatment
Myocardial Infarction	RR (95% CI): 0.96 (0.41, 2.27) during safety emergent period
Stroke	RR (95% CI): 0.48 (0.14, 1.67) during safety emergent period
HRQoL	
SF-36 Physical Functioning	LSMD (95% CI): -1.28 (-2.42, -0.15) averaged over weeks 12 to 28
SF-36 Vitality	LSMD (95% CI): -0.46 (-1.66, 0.74) averaged over weeks 12 to 28
Efficacy Outcomes	
Risk of IV Iron Supplementation	**HR (95% CI): 0.45 (0.26, 0.78) in the first 36 weeks**
Mean Change from Baseline in Hb, g/dL	LSMD (95% CI): 0.02 (-0.13, 0.16) averaged over weeks 28 to 36
Harms	
Treatment-Emergent Adverse Events	91.6% vs. 92.5%
Serious Treatment-Emergent Adverse Events	64.7% vs. 61.8%
Discontinuation Due to Treatment-Emergent Adverse Events	**7.7% vs. 3.8%**

DI-CKD: Roxadustat vs. ESA Evidence Rating

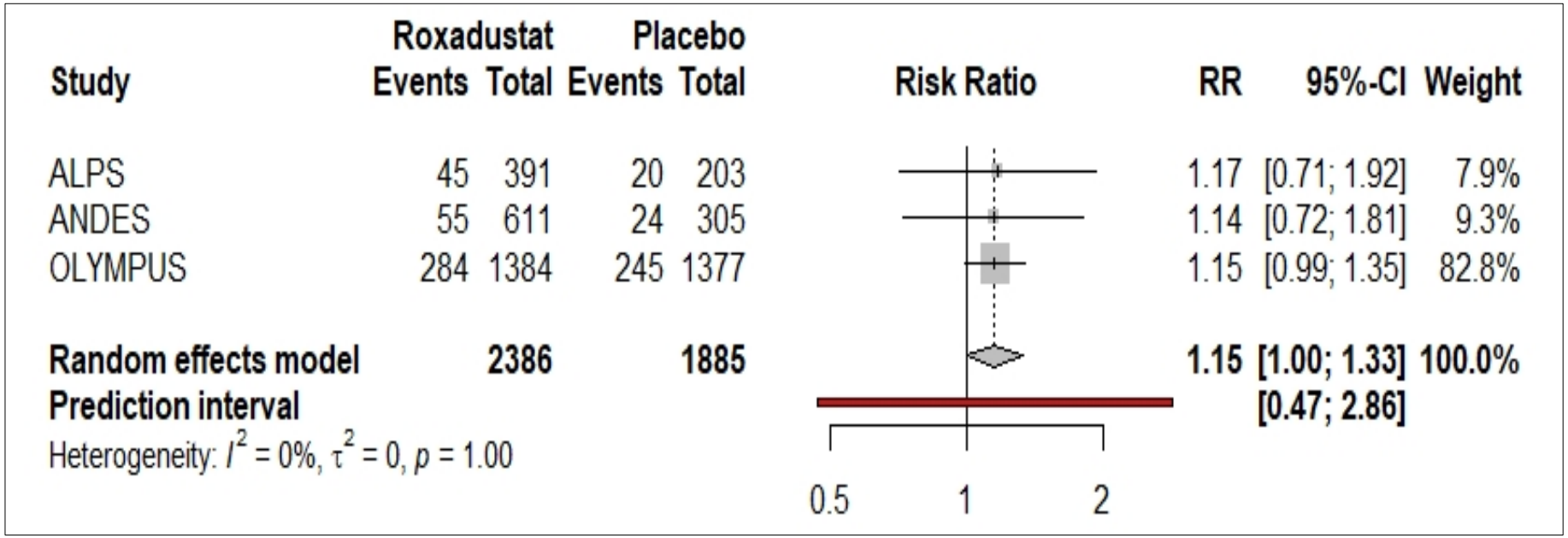
- Roxadustat does not significantly increase Hb, reduce CV safety events, or lead to clinically meaningful differences in HRQoL compared to ESA
- Roxadustat does reduce use of IV iron supplementation
- All-cause mortality: HR: 0.83; 95% CI: 0.50 to 1.38
  - High baseline risk of mortality in this population (11%)
  - Absolute effect range from 5 fewer to 4 additional deaths per 100 patients treated (up to 2 years treatment)
  - This includes a potentially large benefit to large harm
- **Given this uncertainty, we rate the evidence comparing roxadustat to ESAs as *insufficient* (*I*)**

Evidence Map of Key Trials

- DI-CKD
  - Roxadustat vs. ESA (darbepoetin alfa)
    - 1 RCT
- DI-CKD
  - Roxadustat vs. placebo
    - 3 RCTs
- DD-CKD (roxadustat vs. ESA)
  - Roxadustat vs. epoetin alfa
    - 1 Incident DD-CKD
    - 2 Incident and stable DD-CKD
  - Roxadustat vs. darbepoetin alfa and epoetin alfa
    - 1 RCT PYRENEES (stable DD-CKD)

Outcomes	DI-CKD Roxadustat vs. Placebo (ALPS, ANDES, and OLYMPUS)
CV Safety	
MACE	HR (95% CI): 1.08 (0.94, 1.24) during study period
MACE+	HR (95% CI): 1.04 (0.91, 1.18) during study period
All-Cause Mortality	- HR (95% CI): 1.06 (0.91, 1.23) during study period - RR by ICER (95% CI): 1.15 (1.00, 1.33) unclear timepoint
Myocardial Infarction	RR (95% CI): (95% CI): 1.04 (0.71, 1.52) unclear timepoint
Stroke	RR (95% CI): 1.22 (0.62, -2.37) unclear timepoint
Hospitalization	14.57 days/PEY (SD: ±-29.21) vs. 15.89 days/PEY (SD: ±-30.22)‡ at 104 weeks
HRQoL	
SF-36 Physical Functioning	- **LSMD (95% CI): 0.53 (0.05, 1.01) at 12 weeks** - MD by ICER (95% CI): 0.55 (-0.31, 1.40) averaged over week 12 to 28 (1 RCT)
Efficacy	
Risk of Rescue Therapy	**HR (95% CI): 0.19 (0.16, 0.23) in the first 52 weeks**
Risk of Blood Transfusion	**HR (95% CI): 0.26 (0.21, 0.32) in the first 52 weeks**
Risk of IV Iron Supplementation	**- HR (95% CI) at 52 weeks: 0.39 (0.19, 0.81) 1RCT** **- HR (95% CI) at 104 weeks: 0.52 (0.29, 0.99) 1RCT**
Risk of ESA Treatment	**- HR (95% CI) at 52 weeks: 0.08 (0.04, 0.15) 1RCT** **- HR (95% CI) at 104 weeks: 0.10 (0.06, 0.17) 1RCT**
Mean Change from Baseline in Hb, g/dL	**MD (95% CI): 1.63 (0.98, 2.27) averaged over weeks 28 to 52**
Harms	
Treatment-Emergent Adverse Events	RR (95% CI): 1.02 (0.97, 1.06) 2RCTs
Serious Treatment-Emergent Adverse Events	61.6% vs. 56.7%; Event rate per 100 person years: 74.2 vs. 66.0 (1RCT)
Discontinuation Due to Treatment-Emergent Adverse Events or Adverse Events	**RR: 1.38 (1.02, 1.88) (2 RCTs)**

DI-CKD: All-Cause Mortality (Draft Evidence Report)



Comments Received

- Manufacturer stated that this was not counting all deaths and was looking at events rather than time-to-events
  - Pooled HR for mortality: 1.06 (0.91-1.23)
  - Published in Evidence Report
- Comment received on Evidence Report caused us to look further at these results

All-Cause Mortality

- Hazard ratio (HR) is the expected measure; unusual to be very different from relative risk (RR)
- The pooled HR of 1.06 is for all deaths during the study periods, including deaths in patients no longer on therapy
- We believe the RR is up to 28 days after stopping therapy; we do not have the data to pool HRs for this outcome
- We are left with substantial uncertainty about the best estimate of mortality with roxadustat; this increases our uncertainty about the comparison of roxadustat with placebo

DI-CKD: Roxadustat vs. Placebo Evidence Rating

- Roxadustat significantly increases Hb compared to placebo without statistically significantly increasing risk of CV safety events or generally leading to clinically meaningful differences in HRQoL
- Roxadustat reduces need for blood transfusions, rescue therapy with ESAs, and use of IV iron
- We are left with substantial uncertainty about best estimate of mortality with roxadustat; this increases our uncertainty about comparison of roxadustat with placebo
- **Given this uncertainty, we rate evidence comparing roxadustat to placebo as *insufficient* (I)**

Evidence Map of Key Trials

- DI-CKD
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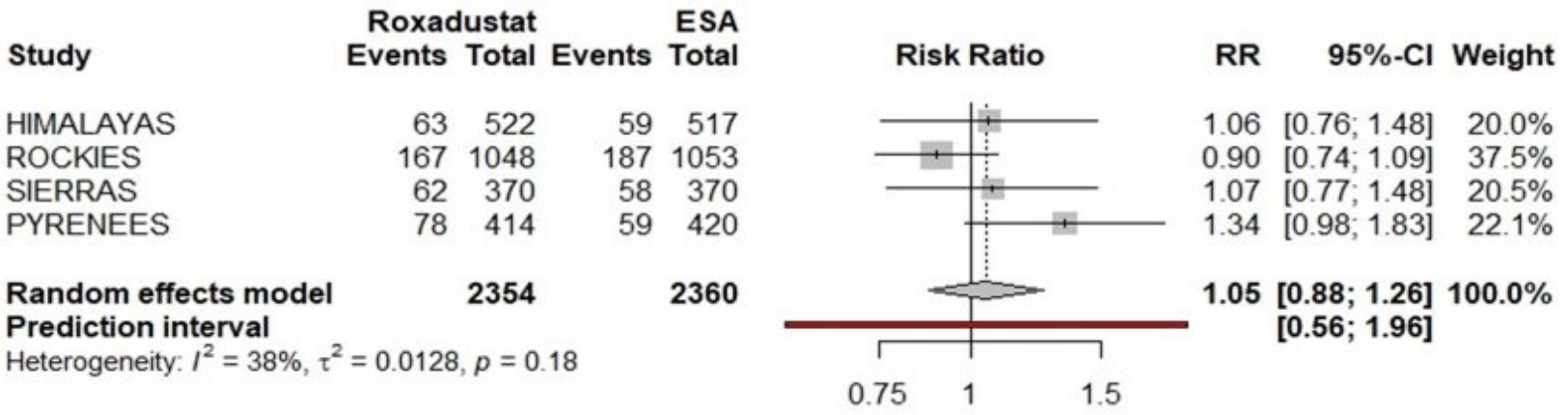
  - Roxadustat vs. epoetin alfa
    - 1 Incident DD-CKD
    - 2 Incident and stable DD-CKD
  - Roxadustat vs. darbepoetin alfa and epoetin alfa
    - 1 RCT PYRENEES (stable DD-CKD)

Outcomes	DD-CKD Roxadustat vs. ESA (HIMALAYAS, ROCKIES, SIERRAS, and PYRENEES)
CV Safety	
MACE	HR (95% CI): 0.96 (0.82, 1.13) in the first 52 weeks*
MACE+	**HR (95% CI): 0.86 (0.74, 0.98) in the first 52 weeks***
All-Cause Mortality	- HR (95% CI): 0.96 (0.79, 1.17) in the first 52 weeks* - RR by ICER (95% CI): 1.05 (0.88, 1.26) unclear timepoint
Myocardial Infarction	- HR (95% CI): 0.95 (0.73, 1.23) in the first 52 weeks* - RR by ICER (95% CI): 1.06 (0.74, 1.52) unclear timepoint
Stroke	- HR (95% CI): 0.90: (0.60, 1.34) in the first 52 weeks* - RR by ICER (95% CI): 0.86 (0.45, 1.63) unclear timepoint
Hospitalization	- HR (95% CI): 1.15 (0.94, 1.41) at end of treatment (PYRENEES) - Mean hospital days ± SD: 12.19 ± 34.12 vs. 7.87 ± 22.95 (PYRENEES)
HRQoL	
SF-36 Physical Functioning	LSMD (95% CI): 0.21 (-0.65, 1.06) averaged over weeks 12 to 28 (PYRENEES)
SF-36 Vitality	LSMD (95% CI): 0.86 (-0.12, 1.83) averaged over weeks 12 to 28 (PYRENEES)
SF-36 Physical Component	LSMD (95% CI): 0.52 (-0.21, 1.25) averaged over weeks 12 to 28 (PYRENEES)
Efficacy	
Risk of Rescue Therapy	HR (95% CI): 0.98 (0.66, 1.46) at end of treatment (PYRENEES)
Risk of Blood Transfusion	**HR (95% CI): 0.82 (0.679, 0.997) during treatment*** **HR (95% CI): 0.87 (0.57, 1.31) at end of treatment (PYRENEES)**
Mean Monthly IV Iron Use, mg	**MD (95% CI): -24.50 (p=0.0002) at week 45 to 52 (1RCT)** **LSMD (95% CI): -48.70 (-70.3, -27.0) at week 53 to 104 (PYRENEES)**
Mean CFB in Hb, g/dL	MD (95% CI): 0.23 (-0.04, 0.50) averaged over weeks 28 to 52
Harms	
Discontinuation Due to Treatment-emergent Adverse Events or Adverse Events	**RR (95% CI): 1.87 (1.34, 2.63)**

*Excluding PYRENEES

DD-CKD: All-Cause Mortality



DD-CKD: Roxadustat vs. ESA Evidence Rating

- Data for most endpoints are only available in pooled analyses that exclude PYRENEES
- 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
- Roxadustat reduced risk of MACE+ in a pooled analysis that excluded PYRENEES
- Roxadustat appears to reduce use of blood transfusion and IV iron supplementation
- All-cause mortality: RR: 1.05; 95% CI: 0.88 to 1.26
  - High baseline risk of mortality in this population (15%)
  - Absolute effect could range from 2 fewer to 4 additional deaths per 100 patients treated (timeframe between 1 and 4 years of treatment).
- **Given this uncertainty, we rate the evidence comparing roxadustat to ESA as *insufficient* (*I*)**

DD-CKD Subgroups: Incident vs. Stable

- The results of the pooled analysis ID-CKD (1 RCT + 10-20% of 2 RCTS)
- A significant reduction in the risk of MACE and MACE+
  - 1 RCT drove the pooled effect estimate for MACE and MACE+
- Lack of reported data about stable DD-CKD in 2 trials prohibited pooling MACE and MACE+ in stable DD-CKD, which theoretically could have had an increase in risk of MACE and MACE+
- We are uncertain about a subgroup effect

Certainty Rating

- DI-CKD
  - Roxadustat vs. ESAs (*insufficient* "*I*")
- DI-CKD
  - Roxadustat vs. placebo (insufficient "I")
- DD-CKD
  - Roxadustat vs. ESAs (*insufficient* "*I*")

Controversies and Uncertainties

- Patients with known HF, MI, ACS, stroke, seizure, or a VTE within 12 weeks, and uncontrolled HTN were excluded from trials—subgroups of particular interest given known harms from ESAs in these populations
- It is uncertain whether increases in CV risk seen in older trials of ESAs were due to higher Hb levels vs. higher ESAs doses of ESAs
- Lack of reported data on quality of life and functional status further limits our ability to assess impact of roxadustat on these outcomes

Potential Other Benefits and Contextual Considerations

- Novel mechanism of action
- An oral option likely important – DI-CKD and home dialysis patients
  - For patients receiving in-center HD, an infused option in dialysis is likely easier
- Higher prevalence of CKD in African American and Latinx community

Public Comments Received

- Mortality in DI-CKD: Roxadustat vs. placebo
- In PYRENEES: Two different ESAs
  - ESAs have been shown to have similar efficacy and safety profiles
- ESA hyporesponsiveness and inflammation
- Difference in protocols between roxadustat and control arms: ESAs were used as part of rescue therapy for roxadustat arm

Questions

Presentation of the Economic Model

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Key Review Team Members

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- Jonathan D. Campbell, PhD, MS, Senior Vice President for Health Economics, ICER

Disclosures:

Financial support was provided to the University of Washington from the Institute for Clinical and Economic Review.

University of Washington researchers have no conflicts to disclose defined as more than $10,000 in health care company stock or more than $5,000 in honoraria or consultancies relevant to this report during the previous year from health care technology manufacturers or insurers.

Objective

Estimate cost effectiveness of roxadustat for the treatment of anemia in patients with CKD compared with ESAs in two populations:

- DI-CKD
- DD-CKD

Methods in Brief

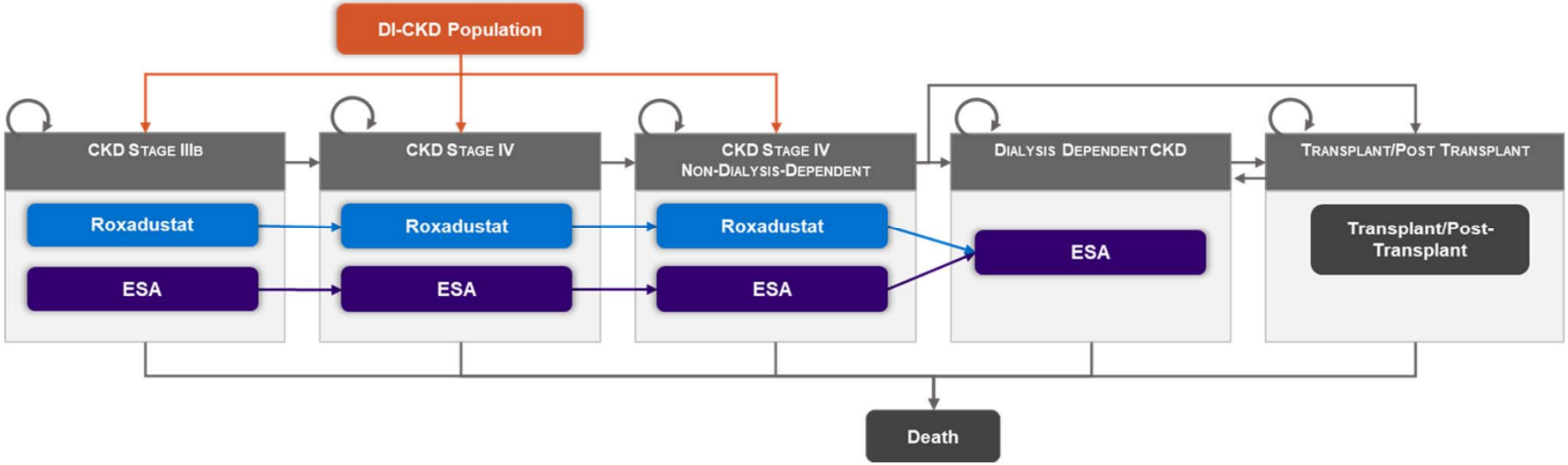
Methods Overview

- **Model**: Markov
- **Setting**: United States
- **Perspective**: Health Care Sector Perspective
- **Population:** CKD patients with anemia
  - DI-CKD Stages IIIb to V
  - DD-CKD
- **Time Horizon**: Lifetime
- **Discount Rate**: 3% per year (costs and outcomes)
- **Cycle Length**: 4 weeks
- **Primary Outcomes**: Quality-adjusted life years (QALYs); life years (LYs); equal value life years (evLYs)
- **Other Outcomes:** MACE+ events, RBC transfusions, use of IV iron

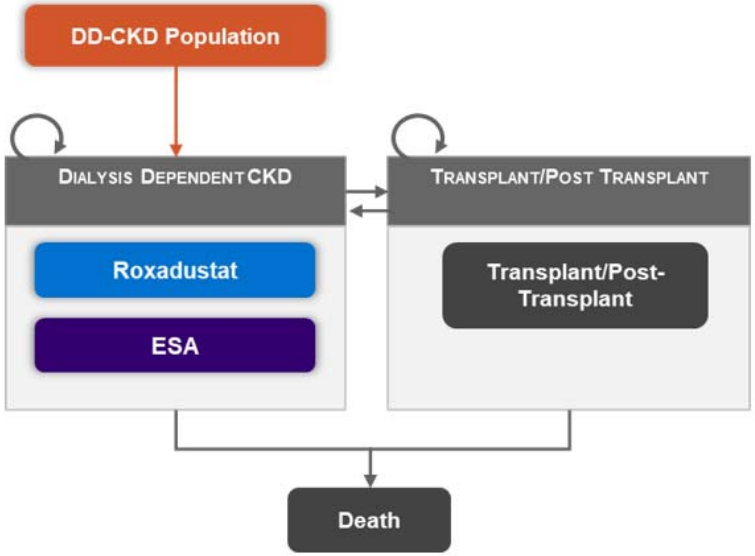
Due to (*insufficient* ["I"]) rating vs. ESAs, cost per QALY ratios were not calculated

Model Schematic: DI-CKD

- Transition probabilities between CKD stages and death based on prior published models of CKD or data from USRDS
  - Probability of death in DD-CKD based on roxadustat Phase III trials



Model Schematic: DD-CKD



Payer Perspective in DD-CKD Population

- Two payment models considered in **DD-CKD** population
  1. Commercial (ASP pricing)
  2. Medicare (bundled payment system)
     - ESAs, IV iron, and RBC transfusions included in bundled payment system
     - Roxadustat modeled as an additional add-on cost for 3 years, after which it was included in bundle at no extra cost

Key Model Assumptions

- Progression of underlying CKD based on published transition probabilities
  - Assume no direct impact of anemia treatment on CKD progression
- Equivalent efficacy and safety across ESAs
- DI-CKD patients use subcutaneously administered forms of ESAs
- DI-CKD patients treated with roxadustat switch to ESAs upon progression to DD-CKD
- No impact on mortality or MACE+ events modeled in DI-CKD population in base case

Key Model Inputs: Hb

- Relative efficacy of roxadustat vs. ESAs based on:
  - DI-CKD: Head-to-head trial vs. darbepoetin alfa
  - DD-CKD: Meta-analysis of 4 trials of roxadustat vs. ESA

Mean Change from Baseline in Hb

Population	Difference (Roxadustat - ESA)
DI-CKD	0.015 (-0.13, 0.16)
DD-CKD	0.23 (-0.04, 0.50)

Key Model Inputs: Annual Treatment Costs

- DI-CKD: Average ESA utilization based on use of pre-filled syringes at a representative dose for each ESA
- DD-CKD: Utilization based on units per cycle for epoetin alfa, converted to darbepoetin alfa

Costs	Commercial	Medicare
Roxadustat	Placeholder price of $13,000 per year with a 50% discount (**$6,500**)	Placeholder price of $13,000 per year with a 50% discount (**$6,500**) **for 3 years**
ESAs Market basket of darbepoetin alfa, epoetin alpha (Epogen), epoetin alfa (Procrit), epoetin alfa, epoetin beta	DI-CKD (WAC): **$7,943** DD-CKD (ASP + 9.5%): **$6,934**	**$0**

Key Model Inputs: Health State Costs

Costs	Cost	Source
Annual Cost of DI-CKD Stage IIIb	$22,000	1
Annual Cost of DI-CKD Stage IV and V	$33,000	1
Annual Cost of DD-CKD	$89,953	2
Transplant Event	$19,636	3
Annual Cost Post-Transplant, Functioning Graft	$26,988	2

1. USDRS. Annual Data Report. 2018. Table F7.2. https://www.usrds.org/annual-data-report/previous-adrs/.
2. USDRS. Annual Data Report. 2019. https://www.usrds.org/media/1300/2019-referencetables_cost.xlsx.
3. CMS IPPS October 2020. MS-DRG 652. https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/AcuteInpatientPPS/FY2020-IPPS-Final-Rule-Home-Page-Items/FY2020-IPPS-Final-Rule-Tables.

Key Model Inputs: Utilities

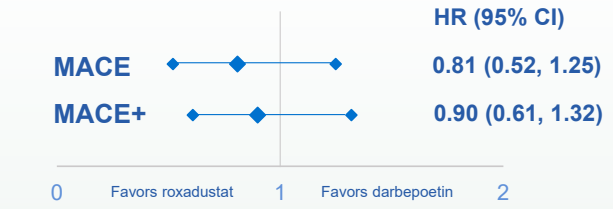
Health State	Utility	Source
Baseline DI-CKD Stage III (without Anemia)	0.82	1
Baseline DI-CKD Stage IV/V (without Anemia)	0.72	1
Baseline DD-CKD ESRD (without Anemia)	0.61	2
Post Transplant	0.74	3
Utility Loss per 1 g/dl Decrease in Hb	0.0114	4

1. Nguyen NTW, et al. 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.
2. Manns B, et al. Quality of life in patients treated with hemodialysis or peritoneal dialysis: what are the important determinants? *Clin Nephrol.* 2003;60(5):341-51.
3. Laupacis A, et al. A study of the quality of life and cost-utility of renal transplantation. *Kidney Int.* 1996;50(1):235-42.
4. Finkelstein FO, et al. Health-related quality of life and hemoglobin levels in chronic kidney disease patients. *Clin J Am Soc Nephrol*. 2009;4(1):33-8.

MACE+

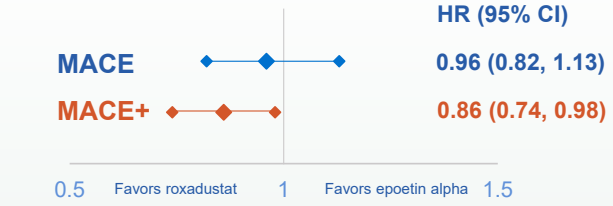
- No statistically significant difference in MACE or MACE+ for roxadustat vs. ESAs in DI-CKD population
- Reduction in MACE+ events in the pooled analysis of 3 Phase III trials vs. ESAs (*excluding PYRENEES*)

Roxadustat DI-CKD Phase III Trial vs. ESA[1]



- No statistically significant difference vs. ESAs
- Impact of MACE+ excluded from base case

Roxadustat DD-CKD Phase III Trials (excludes PYRENEES)[2]



- Statistically significant difference for MACE+
- Will be included in the model

*MACE defined as all-cause mortality/stroke/MI.
†MACE+ defined as all-cause mortality/stroke/MI/unstable angina requiring hospitalization/congestive heart failure.

1. Barratt J, et al. DOLOMITES. ERA-EDTA. June 6-9, 2020. Virtual Congress
2. Provenzano R, et al. Pooled Results. American Society of Nephrology Kidney Week, November 5-10, 2019, Washington DC, USA.

MACE+

- Constant per-cycle risk of each MACE+ event
- Base case for DD-CKD population and scenario in DI-CKD population

RR (95% CI) for MACE+ vs. ESAs	DD-CKD
All-Cause Mortality	1.05 (0.88, 1.26)[1]
Myocardial Infarction	0.95 (0.73, 1.23)[2]
Stroke	0.90 (0.60, 1.34)[2]
Unstable Angina	0.82 (0.44, 1.52)[2]
Heart Failure Hospitalization	0.72 (0.58, 0.91)[2]

1. ICER-conduced meta-analysis of all four Phase III trials of HIMALAYAS, ROCKIES, PYRENEES, and SIERRAS
2. Calculated based on event rates in Provenzano R, et al. Pooled Results. American Society of Nephrology Kidney Week, November 5-10, 2019, Washington DC, USA

Cost and Disutility for MACE+ Events

RR (95% CI) for MACE+ vs. ESAs	Cost	Disutility
Death	$24,669[1]*	Utility of 0 applied to death state
Hospitalization for CHF	$7,807[4]	-0.089[3]
MI Event	$54,785[1]*	-0.042[2]
Unstable Angina Event	$27,713[1]*	-0.041[2]
Stroke Event	$16,980[1]*	-0.204[2]
Post-MI Cycles	$1,790[1]*	-0.011[3]
Post-Stroke Cycles	$430[1]*	-0.101[3]

*Original 2007 values inflated to 2020 US dollars using the PHC Expenditure deflator up to 2017 and then the PCE price index to update to 2020.

1. O'Sullivan AK, et al. Cost estimation of cardiovascular disease events in the US. *Pharmacoeconomics.* 2011;29(8):693-704.
2. Sullivan PW, et al. Preference-based EQ-5D index scores for chronic conditions in the United States. *Med Decis Making*. 2006;26(4):410-20.
3. Shao H, et al. Estimating quality of life decrements due to diabetes complications in the United States: The health utility index (HUI) diabetes complication equation. *Pharmacoeconomics.* 2019;37(7):921-929.
4. CMS Payment for DRG 291

RBC Transfusions

- Utilization of RBC transfusions from Phase III trials
- Cost per transfusion: Administration ($35.73) + 1 unit of blood @ $550.46

RBC Transfusions Over 52 Weeks

	ESAs	HR (95% CI) for Roxadustat vs. ESAs
DI-CKD	5.2%[2†]	1[2†]
DD-CKD	12.8%[1]	0.82 (0.679, 0.997)[1]

†Assumed equal to roxadustat based on findings of a Phase 3 head-to-head non-inferiority study

1. Provenzano R, et al. Pooled Results. American Society of Nephrology Kidney We(ek, November 5-10, 2019, Washington DC, USA.
2. Barratt J, et al. DOLOMITES. ERA-EDTA. June 6-9, 2020. Virtual Congress.

IV Iron

- Utilization of IV iron from Phase III trials
- Cost of IV iron: Administration ($72.18) + drug cost ($89.86)

Use of IV Iron

	ESAs	Difference for Roxadustat vs. ESAs
DI-CKD	21.2 infusions per 100 person-years[1†]	HR (95% CI) 0.45 (0.26, 0.78)[1†]
DD-CKD	44.0 ± 88.6 mg per month[2]	LSM difference (95% CI) 31.9 (41.4, -22.4)[2]

1. Barratt J, et al. DOLOMITES. ERA-EDTA. June 6-9, 2020. Virtual Congress.
2. Esposito C, Csiky B, Tataradze A, Reusch M, Han C, Sulowicz W. Two phase 3, multicenter, randomized studies of intermittent oral roxadustat in anemic CKD patients on (PYRENEES) and not on (ALPS) dialysis. ANS 2019; 2019; Washington, D.C.

Results

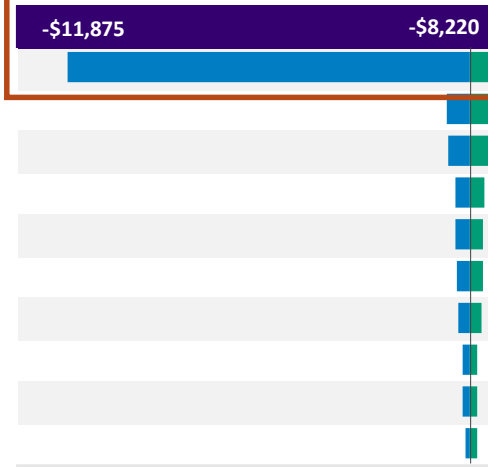
Base-Case Results, DI-CKD

- No difference between roxadustat and ESAs for proportion of patients with Hb level ≥10 g/dL, RBC transfusions, or MACE+
- Negligible differences in outcomes; $8,000 in cost savings with roxadustat **at assumed placeholder price**

Drug	Cost	QALYs	Life Years
ESAs	$430,000	5.38	7.64
Roxadustat	$422,000	5.38	7.64
Incremental	-$8,220	<0.01	0.00

One Way Sensitivity Analyses, DI-CKD

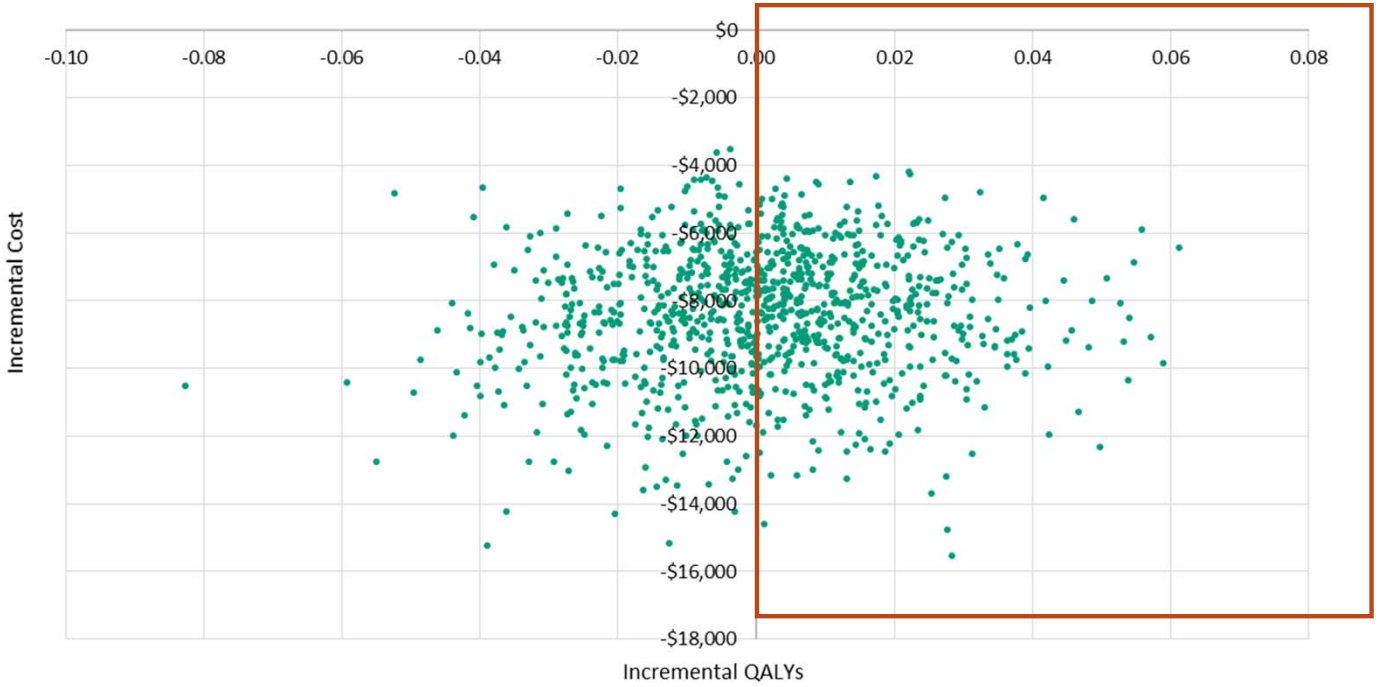
Incremental Total Cost of Roxadustat vs. ESAs



Parameter	Base Case	Low Value	High Value
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
Discount rate for costs	0.23%	0.21%	0.0
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

Probabilistic Sensitivity Analysis

Incremental Cost and QALYs for Roxadustat vs. ESAs, DI-CKD, Commercial Perspective



Likely lower cost

54% of iterations had improved outcomes with roxadustat

Scenario Analyses, DI-CKD

	Incremental Cost	Incremental QALYs
Base Case	-$8,220	<0.01
Modified Societal Perspective	-$9,416	<0.01
Considering Potential Impact on MACE+	$24,000	0.46

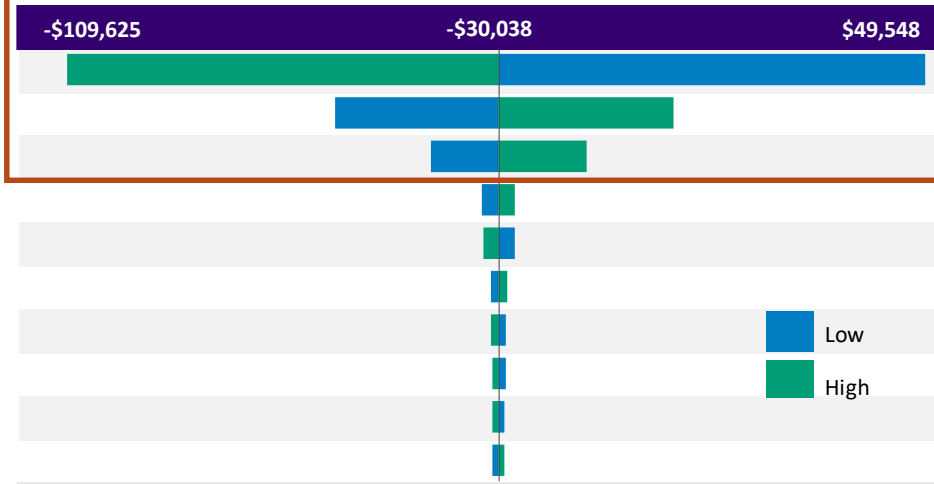
Base-Case Results, DD-CKD

- Fewer LYs and QALYs with roxadustat
- Lower cost for roxadustat **based on assumed placeholder price**
  - Fewer RBC transfusions
  - Reduction in some individual MACE+ events using point estimates

Drug	Commercial Cost	Medicare Cost	QALYs	Life Years	evLY
ESAs	$834,000	$978,000	3.84	6.35	3.84
Roxadustat	$804,000	$957,000	3.75	6.18	3.75
Incremental	-$30,000	-$22,000	0.09	-0.17	-0.09

One Way Sensitivity Analyses, DD-CKD

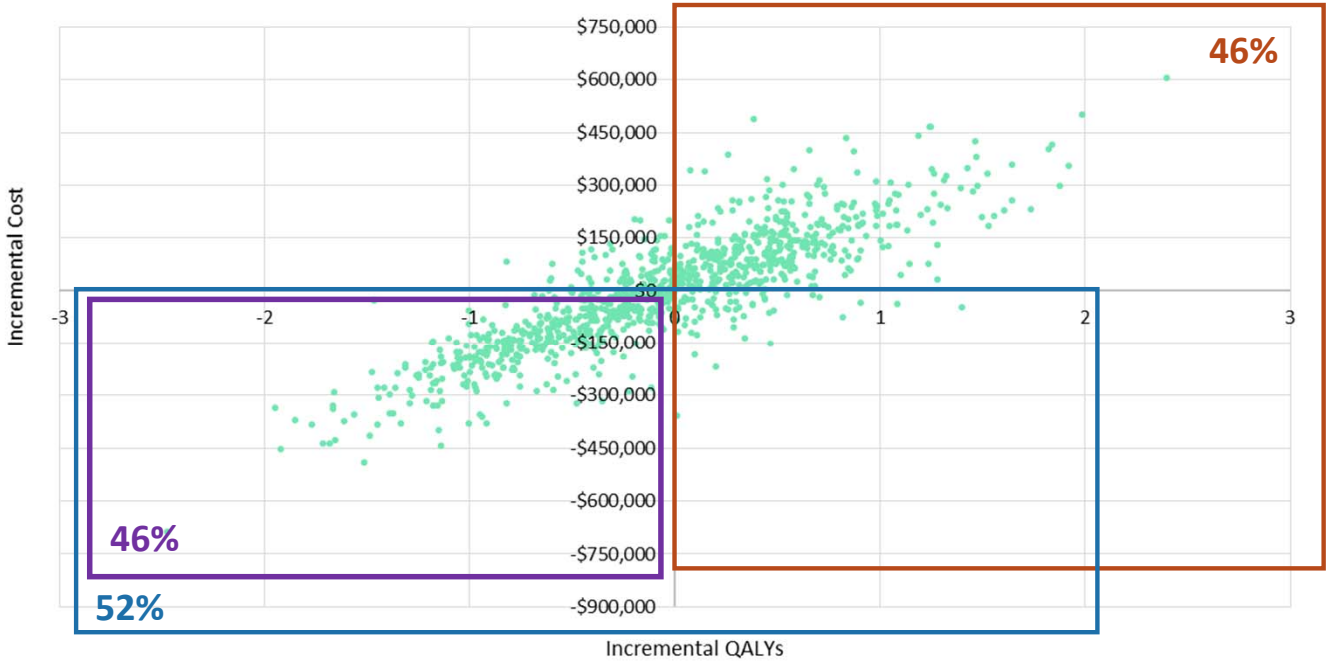
Incremental Total Cost of Roxadustat vs. ESAs



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

Probabilistic Sensitivity Analysis

Incremental Cost and QALYs for Roxadustat vs. ESAs, DI-CKD, Commercial Perspective



Considerable uncertainty in both incremental cost and incremental outcomes

Scenario Analyses, DD-CKD

Commercial	Incremental Cost	Incremental QALYs
Base Case	-$30,000	-0.09
Modified Societal Perspective	-$41,000	-0.09
No Impact on MACE+	$1,600	0.01

Medicare	Incremental Cost	Incremental QALYs
Base Case	-$22,000	-0.09
Modified Societal Perspective	-$32,000	-0.09
No Impact on MACE+	$14,000	0.01

Limitations

- Limited published data for roxadustat
- Heterogeneity in patient symptoms at specific Hb levels
- Model does not fully capture all potential benefits
  - Impact of RBC transfusions on transplant outcomes
  - Availability of an oral treatment option

Comments Received

- Eliminate CKD health state costs and/or emphasize that less costly treatments do not necessarily lead to greater value or gain in lives
- Provide greater emphasis on uncertainty and PSA results
- Limited published data for roxadustat and pending guidance on eligibility and reimbursement for roxadustat via TDAPA
- Analyses do not explore the cost effectiveness of roxadustat in subgroup of patients with incident dialysis
- Model does not capture full impact of rescue therapy with IV iron and RBC transfusion

Conclusions

Roxadustat may be cost-saving assuming a price of $6,500 per year, ***but***:

- With a high degree of uncertainty
- With a potential mortality consequence

DI-CKD

- Similar health outcomes
- Cost savings driven by lower incremental cost vs. ESAs and IV iron

DD-CKD

- Potentially worse health outcomes
- Some reduction in cost from RBC transfusions and iron, but primarily through increased mortality, thus less time spent in CKD health states

Questions

Break

Meeting will resume at 10:35 AM

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Manufacturer Public Comment and Discussion

Manufacturer Public Commenters

Speaker	Title	Affiliation
Dustin Little, MD	Global Clinical Lead, Renal	AstraZeneca
Jeffrey Petersen, MD, FRCP	Global Development Lead	Amgen

Public Comment and Discussion

Stephanie Frilling, MBA, MPH, M. Bioethics
Principal, Policy Analysis and Operations, LMI

Conflicts of Interest:

- *Full-time employee of LMI.*

Lunch

Meeting will resume at 11:55 AM

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Voting Questions

1. Given currently available evidence, in patients who have DI-CKD, is the evidence adequate to demonstrate the net health benefit of roxadustat is superior to that provided by usual care (estimated by placebo arms)?

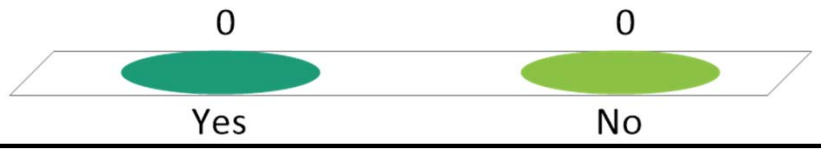
A. Yes

B. No

2. Given currently available evidence, in patients who have DI-CKD, is the evidence adequate to distinguish the net health benefit between roxadustat and ESAs?

A. Yes

B. No



3. Given currently available evidence, in patients who have DD-CKD, is the evidence adequate to distinguish the net health benefit between roxadustat and ESAs?

A. Yes

B. No

3a. If the answer to Q3 is Yes: Based on the available evidence in patients who have DD-CKD, which therapy has a greater net health benefit: a) roxadustat, or b) ESAs?

A. Roxadustat

B. ESAs

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

1 (Suggests Lower Value)	2 (Neutral)	3 (Suggests Higher Value)
DI-CKD: Uncertainty or overly favorable model assumptions creates significant risk that base-case cost-effectiveness estimates are too optimistic.		DI-CKD: Uncertainty or overly unfavorable model assumptions creates significant risk that base-case cost-effectiveness estimates are too pessimistic.
DD-CKD: Uncertainty or overly favorable model assumptions creates significant risk that base-case cost-effectiveness estimates are too optimistic.		DD-CKD: Uncertainty or overly unfavorable model assumptions creates significant risk that base-case cost-effectiveness estimates are too pessimistic.
Very similar mechanism of action to that of other active treatments.		New mechanism of action compared to that of other active treatments.
Delivery mechanism or relative complexity of regimen likely to lead to much lower real-world adherence and worse outcomes relative to an active comparator than estimated from clinical trials.		Delivery mechanism or relative simplicity of regimen likely to result in much higher real-world adherence and better outcomes relative to an active comparator than estimated from clinical trials.
This intervention will not differentially benefit a historically disadvantaged or underserved community.		This intervention will differentially benefit a historically disadvantaged or underserved community.
Small health loss without this treatment as measured by absolute quality-adjusted life year (QALY) shortfall.		Substantial health loss without this treatment as measured by absolute QALY shortfall.
Small health loss without this treatment as measured by proportional QALY shortfall.		Substantial health loss without this treatment as measured by proportional QALY shortfall.
Will not significantly reduce the negative impact of the condition on family and caregivers vs. the comparator.		Will significantly reduce the negative impact of the condition on family and caregivers vs. the comparator.
Will not have a significant impact on improving return to work and/or overall productivity vs. the comparator.		Will have a significant impact on improving return to work and/or overall productivity vs. the comparator.
Other		Other

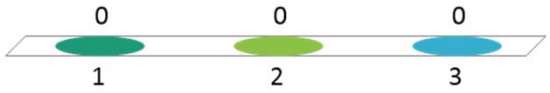
4a. Please vote 1, 2, or 3 on the following potential other benefits and contextual considerations; for questions where a comparator or existing therapy is implied, please answer for roxadustat compared to ESAs. Refer to the table below.

A. 1

B. 2

C. 3

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



4b. Please vote 1, 2, or 3 on the following potential other benefits and contextual considerations; for questions where a comparator or existing therapy is implied, please answer for roxadustat compared to ESAs. Refer to the table below.

A. 1

B. 2

C. 3

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

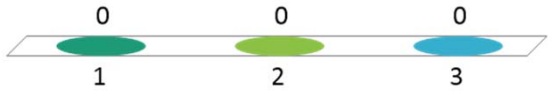
4c. Please vote 1, 2, or 3 on the following potential other benefits and contextual considerations; for questions where a comparator or existing therapy is implied, please answer for roxadustat compared to ESAs. Refer to the table below.

A. 1

B. 2

C. 3

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



4d. Please vote 1, 2, or 3 on the following potential other benefits and contextual considerations; for questions where a comparator or existing therapy is implied, please answer for roxadustat compared to ESAs. Refer to the table below.

A. 1

B. 2

C. 3

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

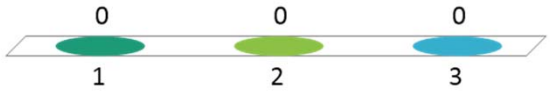
4e. Please vote 1, 2, or 3 on the following potential other benefits and contextual considerations; for questions where a comparator or existing therapy is implied, please answer for roxadustat compared to ESAs. Refer to the table below.

A. 1

B. 2

C. 3

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



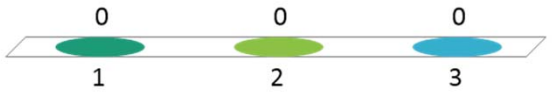
4f. Please vote 1, 2, or 3 on the following potential other benefits and contextual considerations; for questions where a comparator or existing therapy is implied, please answer for roxadustat compared to ESAs. Refer to the table below.

A. 1

B. 2

C. 3

1 (Suggests Lower Value)	2 (Neutral)	3 (Suggests Higher Value)
Small health loss without this treatment as measured by absolute quality-adjusted life year (QALY) shortfall.		Substantial health loss without this treatment as measured by absolute QALY shortfall.



4g. Please vote 1, 2, or 3 on the following potential other benefits and contextual considerations; for questions where a comparator or existing therapy is implied, please answer for roxadustat compared to ESAs. Refer to the table below.

A. 1

B. 2

C. 3

1 (Suggests Lower Value)	2 (Neutral)	3 (Suggests Higher Value)
Small health loss without this treatment as measured by proportional QALY shortfall.		Substantial health loss without this treatment as measured by proportional QALY shortfall.

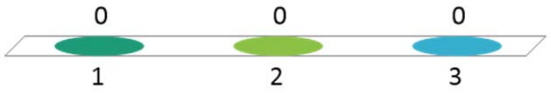
4h. Please vote 1, 2, or 3 on the following potential other benefits and contextual considerations; for questions where a comparator or existing therapy is implied, please answer for roxadustat compared to ESAs. Refer to the table below.

A. 1

B. 2

C. 3

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



4i. Please vote 1, 2, or 3 on the following potential other benefits and contextual considerations; for questions where a comparator or existing therapy is implied, please answer for roxadustat compared to ESAs. Refer to the table below.

A. 1

B. 2

C. 3

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

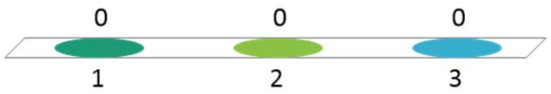
4j. Please vote 1, 2, or 3 on the following potential other benefits and contextual considerations; for questions where a comparator or existing therapy is implied, please answer for roxadustat compared to ESAs. Refer to the table below.

A. 1

B. 2

C. 3

1 (Suggests Lower Value)	2 (Neutral)	3 (Suggests Higher Value)
Other		Other

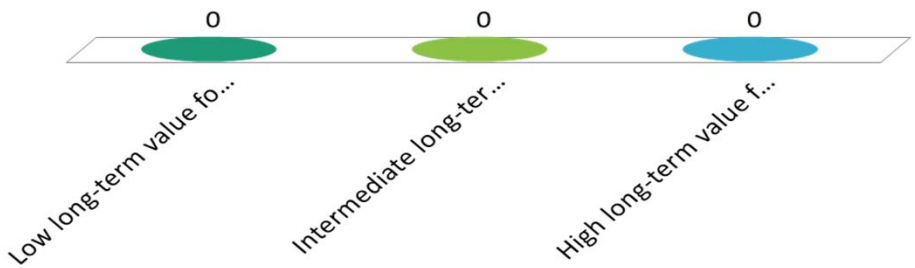


5. Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment at current pricing with roxadustat versus ESAs in patients who have DI-CKD?

A. Low long-term value for money at current pricing

B. Intermediate long-term value for money at current pricing

C. High long-term value for money at current pricing

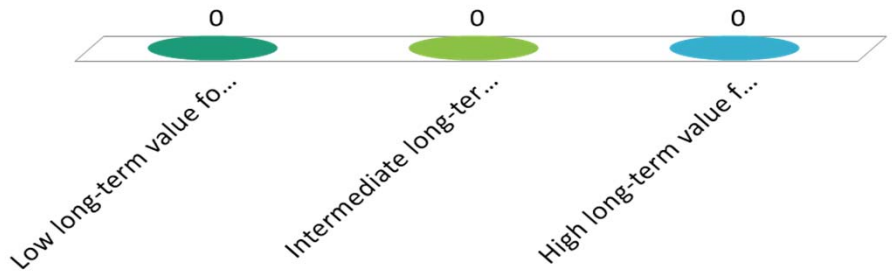


6. Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment at current pricing with roxadustat versus ESAs in patients who have DD-CKD?

A. Low long-term value for money at current pricing

B. Intermediate long-term value for money at current pricing

C. High long-term value for money at current pricing



Policy Roundtable

Policy Roundtable Participant	Title and Affiliation	Conflict of Interest
Jeffrey S. Berns, MD	Professor of Medicine, Associate Chief, Renal Electrolyte and Hypertension, University of Pennsylvania	No conflicts of interest to disclose.
Kerry Cooper, PharmD	Vice President of IPD Analytics	Kerry Cooper is an employee of AstraZeneca.
Leslie Fish, RPh, PharmD	Vice President, Clinical Pharmacy, IPD Analytics	Leslie Fish is an employee of IPD Analytics.
Yola Gawlik, MHA	Executive Director, US Government Affairs and Policy, Amgen	Yola Gawlik is an employee of Amgen.
Patrick O. Gee, Sr., PhD, JLC	Founder & CEHD, iAdvocate, Inc.	No conflicts of interest to disclose.
Pinelopi Kapitsinou, MD	Associate Professor of Medicine, Division of Nephrology and Hypertension, Northwestern University	Dr. Kapitsinou owns equity interests in individual stocks >$10,000 in Biogen, Merck, and Pfizer.
Rosalie Patel, PharmD	Principal Pharmacist, Formulary Strategy and Management	Rosalie Patel is a full-time employee of Blue Shield of California.
Troy Zimmerman	Vice President, Government Relations, National Kidney Foundation	NKF receives more than 25% of its revenue from health care and life sciences companies.

CTAF Reflections

Next Steps

- Meeting recording posted to ICER website next week
- Final Report published on or around March 5, 2021
  - Includes description of CTAF votes, deliberation, policy roundtable discussion
- Materials available at: https://icer.org/assessment/anemia-in-chronic-kidney-disease-2021/.

Adjourn

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