

SUMMARY

Amgen appreciates the opportunity to comment on ICER's *Draft Evidence Report for Treatments for Anemia in Chronic Kidney Disease (CKD)*. It is estimated that at least 6% of the adult population in the U.S. suffers from stage 1 and 2 CKD with an additional 4.5% of the U.S. population in stages three and four.¹ Anemia is common in patients with chronic kidney disease: it is typically observed as early as stage three CKD and is almost universal by stage four. The primary cause of anemia is insufficient production of erythropoietin by the diseased kidneys. Many patients require treatment with erythropoiesis-stimulating agents (ESAs) to manage anemia in CKD. A class of agents, hypoxia-inducible factors prolyl hydroxylase (HIF-PH), including orally administered roxadustat (currently under FDA review), have potentially emerged for the treatment of anemia in CKD.

Amgen is committed to continuing its rich history of discovery, research, and development for treatments for anemia in CKD, including ensuring access for patients. Dialysis-dependent (DD)-CKD has unique considerations as the predominant US reimbursement method is a bundled payment system where existing anemia treatments are not separately paid. We agree that ICER should take the unique bundled Medicare perspective for DD-CKD patients as well as reflect how treatments are reimbursed in the real world (*e.g.*, roxadustat, as a new intervention, will be reimbursed separately from the bundle, as a part of traditional drug add-on payment adjustment (TDAPA)). ICER has modeled the cost-effectiveness of roxadustat, including its relative safety as assessed by all-cause mortality, myocardial infarction (MI), stroke (the composite endpoint for Major Adverse Cardiovascular Events, or "MACE") and additional endpoints of hospitalization for unstable angina or heart failure (the wider composite endpoint than MACE, so-called "MACE+"), in comparison with ESAs. However, ICER's analysis, given modest differences in outcomes, is more akin to a cost-minimization exercise and yet roxadustat's impact on mortality introduces significant uncertainty around this analysis. Based on the data and results of the assessment, we question whether concrete conclusions can be drawn on potential benefits for roxadustat compared with ESAs and would like to highlight a few important recommendations for ICER:

- 1. Revise the analysis and conclusions to recognize that less costly treatments do not necessarily lead to greater value or gain in lives.**
- 2. Revisit the recommendations and reinforce the position that while "*it has been suggested [roxadustat] to be a safer alternative to ESAs, the evidence does not currently support that conclusion*".²**
- 3. Incorporate the FDA label³ and the KDIGO recommendations for ESAs in the roxadustat budget impact analysis.**

Our recommendations are further detailed below.

DETAILED RECOMMENDATIONS

1. Revise the analysis and conclusions to recognize that less costly treatments do not necessarily lead to greater value or gain in lives.

As there were negligible differences in quality-adjusted life year (QALY) outcomes between ESAs and roxadustat, ICER performed a cost minimization exercise, where the increased death rates in the roxadustat arm reduce overall costs, but at the loss of patient lives. One of the biggest drivers for ICER's model is the expected cost-savings calculated as a result of higher mortality rates for patients on roxadustat. While there was no difference in QALYs for the dialysis-independent (DI) population between ESAs and roxadustat, the DD population experienced higher mortality for roxadustat (even with the inclusion of impact on MACE+ in the DD population). ICER states this in the draft evidence report: "*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/yr*3 yrs), primarily attributable to the high mortality rate among patients with DD-CKD.*"⁴ This accounts for nearly a 30 percent reduction in roxadustat costs in the modelled DD-CKD Medicare population (please see Appendix, Table 1 for quotes that show some of the issues that roxadustat faces in this analysis). Medical expenses related to CKD health states such as dialysis, can be costly, such that the implied 'financial benefit' (meaning reduced costs) to the system results from an increase in patient mortality in the model. The notion that patients are therefore likely to incur fewer costs because of less time spent in expensive health states, (*i.e.*, patients are dying rather than moving to better, less expensive health states) is of ethical concern. ICER should revise its model to reflect comparable health costs and moreover, articulate the need for treatments where value lies not only in reduced healthcare system costs but improved patient outcomes.

2. Revisit the recommendations and reinforce the position that while "*it has been suggested [roxadustat] to be a safer alternative to ESAs, the evidence does not currently support that conclusion*".⁵

The potential impact of roxadustat in terms of MACE and MACE+ compared with ESAs is inconclusive for both DI-CKD and DD-CKD populations when comparing risk of mortality. There is insufficient evidence to compare roxadustat with ESAs as confidence intervals related to MACE and MACE+ include the possibility of large clinically important harms or benefits. As alluded to above, in the DI-CKD population, there was no statistically significant difference in QALYs between roxadustat and ESAs. Moreover, in the DD-CKD population, fewer QALYs and equal-value life years (evLYs) were generated with roxadustat. Roxadustat's clinical benefit in the dialysis dependent CKD population, performed worse than Aranesp® (darbepoetin alfa) and Epogen® (epoetin alfa). Underpinning this, in the Supplemental Materials, scatter plots appear to show equal probability that roxadustat will result in additional costs -or- reduced costs.⁶

An additional point related to the conclusions of the report is that the model results reflect significant uncertainty in the results and this should be emphasized throughout the report. Given the lack of conclusive evidence⁷, it is hard to make recommendations for or against roxadustat relative to ESAs where credible range intervals of incremental cost savings/cost expenditure result in ranges of -\$13,000 to -\$5000 for the DI-CKD population, -\$368,000 to +\$329,000

for the DD-CKD commercial population and -\$426,000 to +\$382,000 for the DD-CKD Medicare population.⁸ ICER rated the evidence when comparing roxadustat to ESAs as “I (insufficient)” for both DI and DD populations and this significant uncertainty is really only illustrated in the Supplemental Materials.^{9,10}

3. Incorporate the FDA label¹¹ and the KDIGO recommendations for ESA in the roxadustat budget impact analysis.

ICER uses definitions of anemia (Stauffer and Fan, 2014)¹² that conflict with the current **Kidney Disease Improving Global Outcomes (KDIGO)**¹³ recommendations for ESAs. The evidence to define anemia as hemoglobin (Hb) ≤ 12 g/dL in women or ≤ 13 g/dL in men (Stauffer and Fan, 2014)¹⁴ does not match with the current label for use of ESAs and does not reflect the current treatment/population paradigm. The current FDA label as well as KDIGO recommend commencing ESA treatment when Hb drops below 10 g/dL, reducing or interrupting ESAs as Hb levels approach or exceed 11g/dL. Applying a cutoff of Hb ≤ 10 g/dL, significantly reduces the prevalence of anemia patients eligible for ESAs, and therefore, roxadustat use in comparison to what ICER has currently calculated. Stack *et al.*¹⁵ divides anemia by Hb cutoffs where in Figure 1 (Appendix) shows prevalence of anemia by CKD stage and in accordance with different Hb levels from 10 to 12 g/dL. Instead of the numbers currently in ICER's report (Table 2, Appendix), by this definition:

- **CKD Stage 3 should have only 841k patients eligible for ESAs**
15,873,000 x 0.053 = 841,269
- **CKD Stage 4 & 5 should only have 143K patients eligible for ESAs**
CKD Stage 4 & 5: 1,258,000 x 0.114 = 143,412

Hence, we recommend applying the current FDA mandated Hb threshold to start anemia treatment, such that prevalence will be 5.3% for CKD stage 3 and 11.4% for CKD stages 4 and 5.

CONCLUSION

Amgen values the opportunity to share our insights and hope our recommendations will enhance ICER's analysis in achieving a more balanced view, reflective of real-world clinical practice. ICER has the opportunity to incorporate more reflective costs of treatment that do not penalize patients for reduced mortality from recurrent health state costs; and to reconsider the language used in the draft evidence report due to the limitations of the available evidence. Finally, we advise ICER to utilize more current definitions as defined by the FDA-approved ESA labels and the KDIGO recommendations¹⁶ for ESA use to refine the report's budgetary impact calculations.

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- ² Full Quote: "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." ICER. Draft Evidence Report for the Anemia in Chronic Kidney Disease (CKD) Assessment ICER Anemia in CKD Draft Evidence Report. 2020. Pg.ES2 Line 28-31.
- ³ FDA Drug Safety Communication: Modified dosing recommendations to improve the safe use of Erythropoiesis-Stimulating Agents (ESAs) in chronic kidney disease. FDA: U.S. Food & Drug Administration. 24 June 2011. [Link](#)
- ⁴ ICER. Draft Evidence Report for the Anemia in Chronic Kidney Disease (CKD) Assessment ICER Anemia in CKD Draft Evidence Report. 2020. Pg. 24, Line 8-10.
- ⁵ ICER. Draft Evidence Report for the Anemia in Chronic Kidney Disease (CKD) Assessment ICER Anemia in CKD Draft Evidence Report. 2020. Pg. ES2, Line 29-31.
- ICER. Draft Evidence Report for the Anemia in Chronic Kidney Disease (CKD) Assessment ICER Anemia in CKD Draft Evidence Report. 2020. Page ES2 Line 28-31.
- ⁶ ICER. Draft Evidence Report for the Anemia in Chronic Kidney Disease (CKD) Assessment ICER Anemia in CKD Draft Evidence Report: Supplemental Materials. 2020. Page 138-139.
- ⁷ ICER. Draft Evidence Report for the Anemia in Chronic Kidney Disease (CKD) Assessment ICER Anemia in CKD Draft Evidence Report. 2020. Pg. 17, Line 12.
- ⁸ ICER. Draft Evidence Report for the Anemia in Chronic Kidney Disease (CKD) Assessment ICER Anemia in CKD Draft Evidence Report: Supplemental Materials. 2020. Pg.138, Table E18.
- ⁹ ICER. Draft Evidence Report for the Anemia in Chronic Kidney Disease (CKD) Assessment ICER Anemia in CKD Draft Evidence Report. Supplemental Materials. 2020. Pg.138, Table E18.
- ¹⁰ ICER. Draft Evidence Report for the Anemia in Chronic Kidney Disease (CKD) Assessment ICER Anemia in CKD Draft Evidence Report: Supplemental Materials. 2020. Pg.138-139.
- ¹¹ FDA Drug Safety Communication: Modified dosing recommendations to improve the safe use of Erythropoiesis-Stimulating Agents (ESAs) in chronic kidney disease. FDA: U.S. Food & Drug Administration. 24 June 2011. [Link](#)
- ¹² Stauffer ME, Fan T. Prevalence of anemia in chronic kidney disease in the United States. *PloS one*. 2014;9(1):e84943-e84943.
- ¹³ KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease: Kidney international supplements. Official Journal of the International Society of Nephrology. 2012; 2(4). [Link](#)
- ¹⁴ Stauffer ME, Fan T. Prevalence of anemia in chronic kidney disease in the United States. *PloS one*. 2014;9(1):e84943-e84943.
- ¹⁵ Stack AG, Alghali Ahmed, Li X, Ferguson JP, Casserly LF, Cronin C, et al. Quality of care and practice patterns in anaemia management at specialist kidney clinics in Ireland: a national study. *Clinical Kidney Journal*. 2017;1-9. [Link](#)
- ¹⁶ All references to the KDIGO® guidelines for CKD-MBD set forth herein are intended to be informational only and do not reflect KDIGO®'s endorsement or support of Aranesp®, Epogen® and/or Amgen. KDIGO® is a registered trademark of the National Kidney Foundation, Inc.

APPENDIX

Table 1: Roxadustat is only cost saving due to higher mortality rates among patients, moreover, removal of MACE+ eliminates this

| # | Location | Quote |
|---|--------------------|---|
| 1 | Pg. 24, Line 8-10 | “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.” |
| 2 | Pg. 140, Line 7-10 | Scenario 2 (inclusion of impact of MACE+, DI-CKD): “In this scenario, roxadustat resulted in 0.46 more QALYs due to reduction in mortality and MACE at an incremental cost of \$24,000 versus ESAs higher cost (\$24,000) compared with ESAs. Higher costs were driven by the potential reduction in mortality with roxadustat combined with CKD health state costs.” |

Table 2: ICER’s calculations for Budget Impact

| CKD Stage | CKD Population (% of 37 Million) | Anemia prevalence by stage | Self-reported anemia by stage | ICER’s Assumption 50% of self-reported anemic patients are taking ESAs |
|-----------|----------------------------------|----------------------------|-------------------------------|--|
| 3 | 15.9 million (42.9%) | 2.76 million (17.4%) | 732K (26.5%) | 365,952 |
| 4 | 925K (2.5%) | 466K (50.4%) | 96,500 (20.7%) | 48,252 |
| 5 | 333k(0.9%) | 178K (53.4%) | 76,463 (43%) | 38,232 (DD-CKD) |

Figure 1: Prevalence of Anemia by CKD stage (Stack et al)*

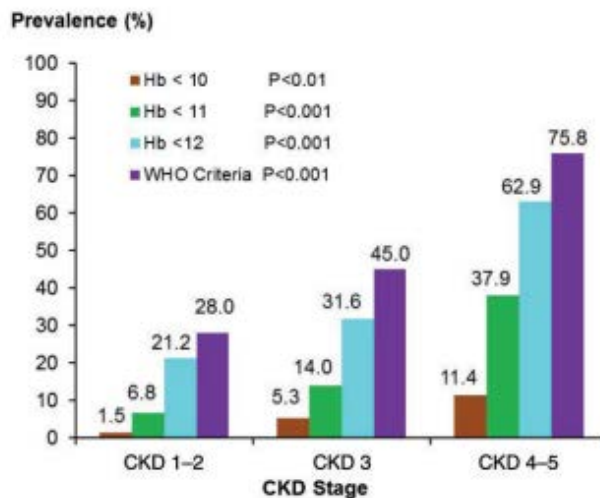


Fig. 1. Prevalence of anaemia by CKD stage.

*Stack AG, Alghali Ahmed, Li X, Ferguson JP, Casserly LF, Cronin C, et al. Quality of care and practice patterns in anaemia management at specialist kidney clinics in Ireland: a national study. *Clinical Kidney Journal*. 2017;1-9. [Link](#)

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December 10, 2020

Steven D. Pearson, MD, MSc
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Re: ICER's Assessment of Treatments for Anemia in Chronic Kidney Disease

Dear Dr. Pearson,

GlaxoSmithKline (GSK) appreciates the opportunity to provide comments in response to the Institute for Clinical and Economic Review's (ICER) Draft Evidence Report for the assessment of treatments of Anemia for Chronic Kidney Disease (CKD). Overall, there are two areas that GSK would like to highlight:

- Definition of hyporesponsiveness to recombinant human erythropoietin (rhEPO); and
- Differences across study protocols for iron supplementation and red blood cell transfusions (RBCT)

1. Definition of hyporesponsiveness to rhEPO


ICER has accepted inflammation status as a subgroup-defining criterion promoting the notion that inflammation equals hyporesponsiveness to rhEPO. While inflammation contributes to hyporesponsiveness, evidence points to multiple factors that may influence hyporesponsiveness.^{1,2} Although there is no universal agreement of the exact definition of hyporesponsiveness, commonly used definitions include: 1) monthly rhEPO dose, 2) monthly rhEPO dose divided by patient weight in kg, and 3) an erythropoietin resistance index (ERI) based on rhEPO dose and baseline hemoglobin³

2. Differences in study protocols for iron supplementation and RBCT

Difference in protocols between roxadustat and control arms for target hemoglobin, RBCT rescue, and iron supplementation are not acknowledged by ICER in this review. Further consideration may need to be given on how to adjust for those differences across placebo^{4,7} and active-controlled^{4,6,7-10} trial results included in this review. Related to this matter, ICER may wish to reflect on how placebo-controlled data will be able to inform the benefit:risk of roxadustat in the real world.

Please feel free to contact us should you wish to discuss these recommendations in further detail.

Sincerely,



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January 5, 2020

Dr. Steven D. Pearson
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Re: Public Comments on Draft Evidence Report

Dear Dr. Pearson,

AstraZeneca and FibroGen appreciate the opportunity to comment on the draft evidence plan for the assessment of roxadustat. Note, on December 18th it was announced that the FDA has requested further clarifying analyses of clinical data, to complete its review of the NDA for roxadustat, an oral hypoxia-inducible factor prolyl hydroxylase (HIF-PH) inhibitor for adult patients with anemia of chronic kidney disease (CKD) on and not on dialysis.¹

AstraZeneca and FibroGen are committed to working with the FDA and have agreed to submit the additional clarifying analyses as soon as possible to assist with the completion of labelling discussions. The NDA remains under regulatory review, with the FDA having set a new action date of March 20, 2021.

AstraZeneca and FibroGen acknowledge that the pivotal trials and pooled analyses—though presented at ASN—were not yet published in peer-reviewed medical journals at the time of ICER’s analysis. This likely limited ICER’s ability to conduct their analyses and appears to have led to significant limitations in meta-analyses performed by ICER (see details below). We are working to publish these data. Of note, the pooled incident dialysis data² and ANDES³ have recently been published electronically. As stated below, we feel that a health economic evaluation of roxadustat may be more appropriate following the full publication of trial results.

Appropriateness of Health Economic Evaluation

An assessment of the available evidence for the evaluation of roxadustat for the treatment of CKD anemia is presented as part of the draft evidence report. The assessment concluded that there are insufficient data available to conduct the health economic evaluation of roxadustat in comparison with ESAs in both non-dialysis dependent and dialysis dependent patients, and promising but inconclusive evidence in comparison with usual care. As a result of these conclusions, ICER considers that there exists no substantive basis to generate a reasonable analysis on the comparative cost-effectiveness of roxadustat, ESA and usual care. Consequently, we question whether the presented health economic evaluation is informative because it is based only on currently publicly available estimates of comparative effectiveness between roxadustat and ESAs, which do not include full publication of roxadustat phase III results, and does not take into account the pending guidance on eligibility and reimbursement for roxadustat via the Transitional Drug Add-on Payment Adjustment (TDAPA) payment system in 2021. A health economic evaluation of

roxadustat may be more appropriate following full publication of trial results and confirmation of TDAPA eligibility.

Meta-Analyses

As part of the extensive global clinical trial program assessing roxadustat for the management of CKD anemia, efficacy and safety results were pooled across dialysis dependent and non-dialysis dependent patient populations to obtain robust estimates of the impact of treatment with roxadustat. The methods of the de novo meta-analyses conducted by ICER and presented in the draft evidence report are inconsistent with the approach agreed to with FDA that is informed by significant experience and key clinical aspects of the treatment of anemia in the specific population of patients with CKD. Importantly, the approach of the FDA takes into account differences in patient time at risk due to asymmetric drop-outs between treatment arms that imposes informative censoring and bias. As was recognized by the FDA, there is no methodology that can control for or avert the bias imposed by informative censoring, however, certain methodologies can minimize the bias and provide a clinically interpretable point estimate that is externally generalizable to the setting outside of clinical trials.

The pooled analysis of the intent-to-treat (ITT) non-dialysis dependent patient populations of ALPS, ANDES, and OLYMPUS utilizes the full duration of follow-up to minimize the informative censoring that was imposed by the inability of the sickest patients with the highest morbidity and mortality rates to tolerate the lack of anemia treatment (i.e. placebo). This is in contrast to analysis conducted from an on-treatment perspective which may bias conclusions against roxadustat as a result of informative censoring. Using the full duration of follow-up in ITT analysis and accounting for time at risk by treatment arm, in the non-dialysis dependent populations of ALPS, ANDES, and OLYMPUS roxadustat was shown to be comparable to placebo in the risk of major adverse cardiovascular events (MACE, hazard ratio [HR]: 1.08; 95% CI: 0.94 to 1.24), MACE+ (HR: 1.04; 95% CI: 0.91 to 1.18), or all-cause mortality (HR: 1.06; 95% CI: 0.91 to 1.23).⁴ This conclusion is further illustrated in Figure 1, which shows no meaningful difference in survival for non-dialysis dependent patients treated with roxadustat or placebo.

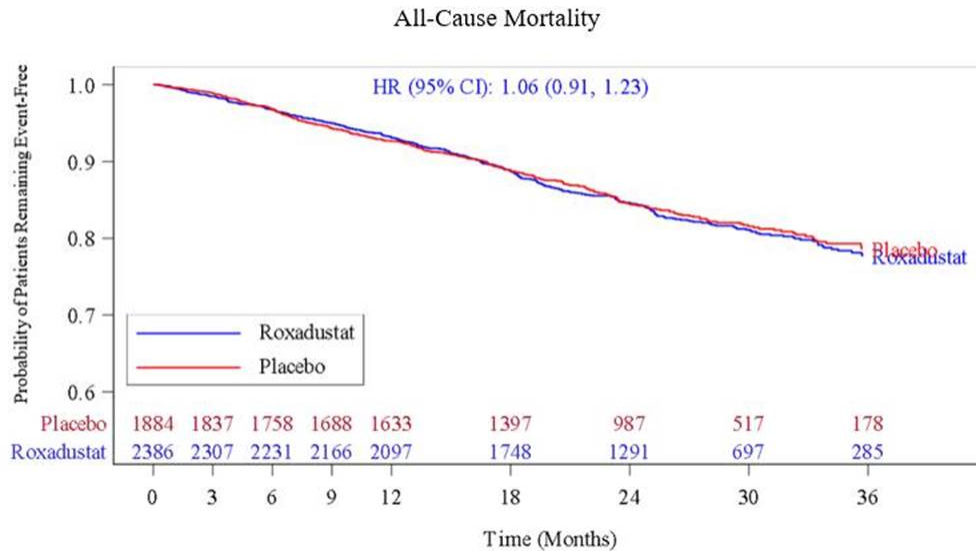


Figure 1. Kaplan-Meier estimate of all-cause mortality in non-dialysis dependent patients treated with roxadustat and placebo.

The ITT analysis agreed to with the FDA correctly captures all observed MACE, MACE+, and death events, and accounts for differences in patient time at risk between the two treatment arms during study follow-up. By contrast, the de novo meta-analysis performed in support of the ICER evaluation and included in the draft report, does not appear to account for time at risk by treatment group. Additionally, we are unable to verify all individual study data used to create the pooled all-cause mortality meta-analysis included in the ICER report, and it appears that the analysis may not have included all deaths for each study.

Due to these methodologic limitations, we consider that the results of the ICER meta-analysis should not be used to assess the value of roxadustat in NDD patients.

We also consider that the meta-analysis presented in the ICER report of all-cause mortality in the DD roxadustat trials is limited, and should not be used to assess the value of roxadustat; due to failure to account for time at risk by treatment group, and due to inclusion of the PYRENEES trial (see below).

Dialysis Dependent Pooled Analysis

Roxadustat has an extensive global clinical trial program, and has been studied in over 10,000 patients.⁵ ICER has conducted a meta-analysis of four dialysis dependent roxadustat clinical trials. In order to conduct a valid meta-analysis, it is important to determine the appropriateness of combining data from different clinical studies. Prior to the FDA filing, it was determined by the FDA that PYRENEES was not an appropriate study to include in the pooled safety and efficacy analyses due to potential heterogeneity and biases introduced by having more than one ESA in the active comparator arm.

In PYRENEES, an exclusively ex-US study, the ESA comparator arm included two different ESA products – epoetin alfa (short-acting) and darbepoetin alfa (long-acting) – that were not randomly assigned and not balanced in terms of sample size.⁶ Per protocol, if patients were randomized to

the ESA treatment arm, those patients who had previously been treated with epoetin alfa continued on epoetin alfa and those previously treated with darbepoetin alfa stayed on darbepoetin alfa as the active comparator. The choice of the ESA product prior to study entry could have been influenced by several factors including reimbursement/medical access issues, practice patterns, patient or dialysis facility differences that were not measured and, therefore, could have introduced bias regarding the clinical outcomes since the assignment to epoetin alfa versus darbepoetin alfa was not randomized. Moreover, there are likely additional confounding variables that cannot be accounted for in the 2 ESA comparator arms due to the lack of randomization. Furthermore, recent literature has suggested that differences in cardiovascular risk may exist between long- and short-acting ESAs,⁷ introducing potential heterogeneity in the active comparator arm that cannot be accounted for. Combining two different types of ESAs limits the ability of the meta-analysis to generalize its results to a larger population without accounting for the exact composition of types of ESA. For these reasons, the FDA stated that they prefer that the safety analysis for PYRENEES was submitted separately instead of as part of the pooled dialysis studies. Due to differences described above, we recommend PYRENEES is not pooled with the other 3 dialysis dependent (DD) studies (e.g., HIMALAYAS, ROCKIES, SIERRAS). Please refer to Provenzano et al. ASN 2019 presentation for more information on results of the pooled analyses of roxadustat cardiovascular safety results from these 3 DD-CKD studies since these analyses form the basis for the current assessment of roxadustat by the FDA.⁴

Furthermore, the proposed analyses do not explore the cost-effectiveness of roxadustat in the subgroup of patients with incident dialysis, where a larger reduction in MACE was observed for patients treated with roxadustat vs. ESA in the incident dialysis population compared with the overall DD population (HR: 0.70 [0.51 to 0.96] vs. 0.96 [0.82 to 1.13]). This is a clinically relevant and critically important population of CKD patients which should be appropriately reflected in the analysis. Notably, the cardiovascular safety results for the pooled incident dialysis population have been recently published electronically.²

Medicare Reimbursement of Dialysis Dependent Patients

Regarding the United States dialysis population, who are largely supported by the Centers for Medicare & Medicaid Services (CMS) End-Stage Renal Disease (ESRD) Prospective Payment System (PPS), it is our position that roxadustat should receive an incentive payment for entering the market as a new innovative drug therapy. We are actively progressing discussions with appropriate parties within CMS ahead of the anticipated PDUFA date.

Medicare will issue guidance on eligibility and reimbursement for roxadustat via the TDAPA payment system in 2021. The intent of the TDAPA, as implemented in 42 CFR 413.234(c), is to facilitate beneficiary access to certain qualifying new ESRD drugs, while treating dialysis organizations gain familiarity with incorporating new products into their practice. Following the TDAPA period, we anticipate that roxadustat will be reimbursed as part of the ESRD bundled base rate. It should be noted that CMS periodically reviews the base rate and may revise the reimbursement based on new cost and utilization data. Given the unique TDAPA reimbursement situation described above for innovative products, we do not believe the comparison of an innovative product, reimbursed through an innovative payment model (TDAPA), to an established product reimbursed through a bundled payment (PPS) is appropriate, nor will it result in meaningful information for decision makers. Such a comparison would ignore the value of innovation in the treatment of CKD, which the government is trying to incentivize, in order that

patients may experience new treatment options. Therefore, we suggest that the long-term cost effectiveness analysis include scenarios which include the drug-acquisition cost of ESA in order to meaningfully compare the cost-effectiveness of roxadustat vs. ESAs in Medicare DD-CKD patients.

Background Costs Associated with CKD Management and Dialysis and Impact of Rescue Therapy

The health economic evaluation of roxadustat should exclude the costs associated with background CKD management and dialysis. As CKD progression and requirements for renal replacement therapy will not differ between treatment arms, these costs represent unrelated future costs that should not be captured in the analysis.⁸ High background management costs present a significant barrier to demonstrating cost-effectiveness in comparison to less efficacious treatments, including the potential for the treatment to be not cost-effective at zero price, which diminishes the value of conducting a cost-effectiveness analysis.

Furthermore, the analysis fails to capture the full impact of rescue therapy with intravenous iron and red blood cell (RBC) transfusion. RBC transfusion can provide immediate, but temporary, relief of anemia symptoms, however, acute risks of transfusion include transfusion reactions, infection-transmission, immunologic sensitization, hyperkalemia, and volume overload.⁹ The longer-term transfusion risk that is important to patients with CKD also includes a decreased likelihood of receiving a kidney transplant, and often results in longer wait time prior to transplantation.¹⁰ Further, following a kidney transplant, patients with history of RBC transfusions have a higher risk of kidney rejection due to alloimmunization¹¹. The requirement for intravenous iron infusion also imposes a significant burden on patients and healthcare providers, particularly in dialysis independent (DI) patients, where patients may require five separate infusions (e.g. iron sucrose) over two-weeks, each incurring additional administration costs.

Data inaccuracies

We would like to note the following transcription errors in the report, so they accurately reflect the publications from which they were referenced.

- In the DD-CKD population, the correct data from the pooled analysis of the three trials in the risk of MACE⁺ should be HR 0.86 (0.74, 0.98); this data was presented at ASN 2019.⁴
- In the DI-CKD population, the MACE pooled data presented by AZ/FibroGen was not for 52 weeks as presented in the report, but for the entire study period.
- We are unable to verify all individual study data used to create the pooled all-cause mortality from the DI-population. As above, we consider that the comparison of mortality risk for roxadustat versus placebo in the DI population should be based on ITT analysis using all deaths reported during the study period, and adjusting for time-at-risk by treatment group.

Both AstraZeneca and FibroGen remain committed to offering a revolutionary treatment option for the benefit of the millions of Americans who suffer from anemia of CKD, and as noted above, we appreciate the chance to offer clarifying comments to the draft evidence plan for the assessment of roxadustat. However, pending the full publication of trial results and the noted limitations of

ICER's meta-analysis, we feel that the presented health economic evaluation is not informative of roxadustat's likely cost-effectiveness when used in clinical practice.

Respectfully,



Kerry Cooper, MD
VP, Medical Affairs Renal
AstraZeneca



Mark Eisner, MD MPH Chief Medical Officer
FibroGen

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Dec 21st, 2020

Steven D. Pearson, MD, MSc
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Submitted via email: publiccomments@icer-review.org

RE: Treatments for Anemia in Chronic Kidney Disease: Effectiveness and Value. *Draft Evidence Report*

Dear Dr. Pearson and ICER CKD team,

On behalf of Pfizer Inc., thank you for the opportunity to comment on the *Treatments for Anemia in Chronic Kidney Disease: Effectiveness and Value, Draft Evidence Report*. Our team has reviewed the draft evidence report. We appreciate ICER's decision to take our suggestion on price correction of Retacrit[®] into consideration. In the report, we have identified few elements that have potential to materially bias the assessment. Below you will find our concerns and suggested modifications for the following area:

1. Incorporation of ASP erosion of ESAs over time

1. Incorporation of ASP erosion of ESAs over time:

We appreciate ICER's choice to adopt the latest ASP in their base case analysis. However, given the time horizon of present analysis was lifetime, we recommend the incorporation of ASP erosion of ESAs over time in the analysis.

To substantiate our request, we want to highlight the quarterly actual Average Sales Price (ASP) of Aranesp[®], Epoetin alfa and Retacrit[®], also known as ASP base price, which excludes the 6% Center for Medicare & Medicaid Services (CMS) add-on payment, between Q4 2018-Q4 2020^{1,2} (Table 1). The annual price decline of Epoetin alfa was 1.2%, 7.6% and 13.8% in 2018, 2019 and 2020, respectively, due to the introduction of biosimilar Epoetin alfa-epbx (Retacrit[®]). If more Epoetin alfa biosimilar products are to enter the US market, the additional competition

may further accelerate price decreases for short-acting ESAs, whereas the price of innovative products (e.g., Roxadustat) that lack competition, in general, is expected to slightly increase over time. Hence, the incremental drug cost differences of ESAs versus Roxadustat observed may decrease over time.

| CMS QTR | Epoetin Alfa | Aranesp | Retacrit |
|---------|--------------|---------|----------|
| 1Q18 | \$11.44 | \$3.68 | N/A |
| 2Q18 | \$12.26 | \$3.57 | N/A |
| 3Q18 | \$12.35 | \$3.62 | \$11.03 |
| 4Q18 | \$11.58 | \$3.56 | \$11.03 |
| 1Q19 | \$11.27 | \$3.62 | \$10.68 |
| 2Q19 | \$11.07 | \$3.74 | \$10.70 |
| 3Q19 | \$10.81 | \$3.61 | \$9.54 |
| 4Q19 | \$10.41 | \$3.63 | \$9.00 |
| 1Q20 | \$9.97 | \$3.60 | \$8.73 |
| 2Q20 | \$9.45 | \$3.46 | \$6.98 |
| 3Q20 | \$9.15 | \$3.57 | \$8.42 |
| 4Q20 | \$8.59 | \$3.51 | \$8.10 |
| 1Q21 | \$8.325 | \$3.357 | \$8.05 |

Table 1 Quarterly ASP of ESAs

Also, there is a distinct pricing dynamic in long-acting versus short-acting ESAs market, and therefore separation the cost estimate of long-acting ESAs from short-acting ESAs may need to be considered when taking ASP erosion into account. As shown in Figure 1, the price of Epoetin alfa drops constantly over time, due to the introduction of biosimilar Epoetin alfa-epbx (Retacrit®), whereas the price of Aranesp® stays stable over time.

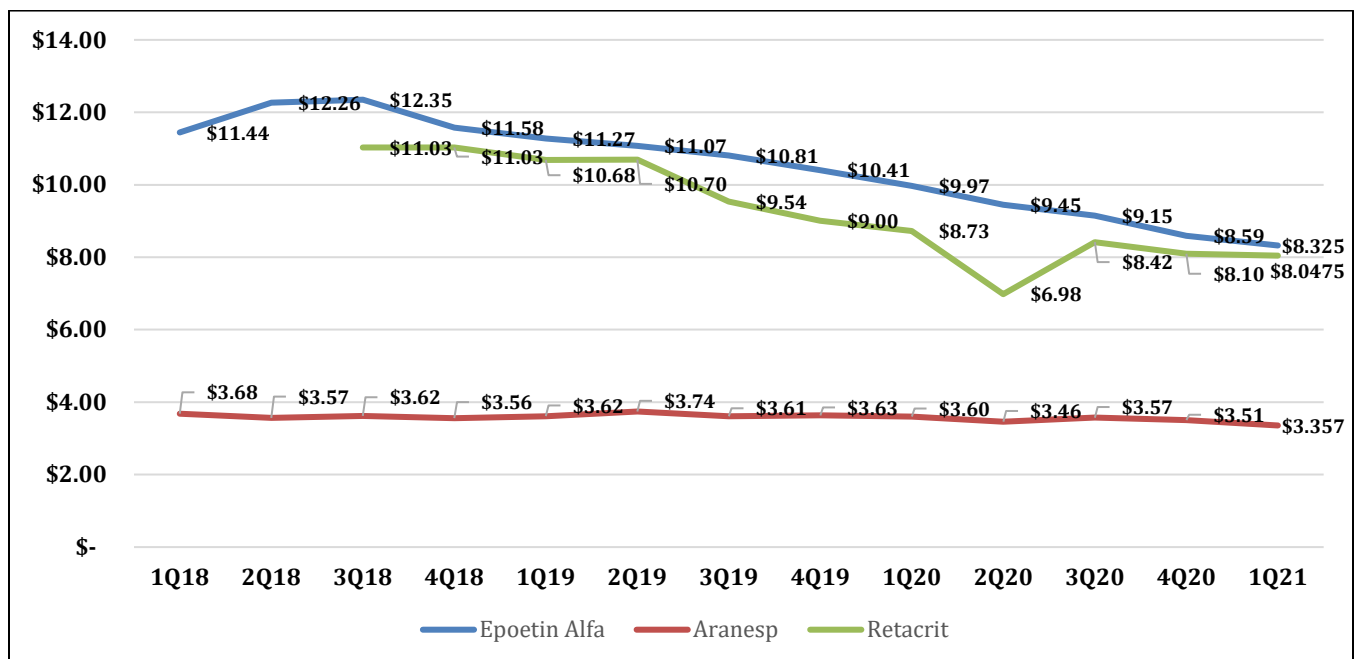



Figure 1 The ASP Trend of ESAs

We strongly recommend ICER to perform a scenario analysis that takes ASP erosion over time into consideration, particularly in the short-acting ESAs market. At the minimum, we recommend that ICER include in their “Limitations” discussion about the uncertainty of drug cost of ESAs over time, which will impact the findings in the present analysis.

Thank you for your attention to our recommendations and for the opportunity to provide additional feedback.

Sincerely,



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Pfizer Inc, 235 East 42 Street, New York, NY 10017



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January 5, 2021

Steven D. Pearson, MD, MSc, FRCP
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RE: Draft Evidence Report “Treatments for Anemia in Chronic Kidney Disease: Effectiveness and Value”

Dear Dr. Pearson:

Patients Rising Now advocates on behalf of patients with serious and chronic conditions and diseases for them to have access to life-improving and life-saving therapies and services. Access to such treatments and services is essential, and it spans affordability, insurance coverage, and physical access. To support improved access, we are committed to engaging patients, caregivers, physicians, media, health policy experts, payers, providers, and others to foster people-centered discussions about the entire U.S. health care system. That is, our goal is a balanced dialogue that illuminates the truth about health care innovations and advancements in a just and equitable way.

We appreciate the opportunity to provide our comments on ICER’s November 30th Draft Evidence Report “Treatments for Anemia in Chronic Kidney Disease: Effectiveness and Value.”

Overall, we find that this report is of very poor quality. The presentation and production of the content, the reliance on uncertain data, and weak understanding of health care financing and reimbursement in the United States has yielded a report with incorrect, misleading, and just plain bad conclusions regarding treatment for anemia in chronic kidney disease (CKD).

Several aspects contributing to the overall poor quality are discussed below, followed by some brief comments about People-Centered Perspectives; Uncertainties and Assumptions; and an Additional Point.

1. The draft report is poorly written, badly organized, and sloppy

ICER’s stated goal is to “to help stakeholders interpret and apply evidence.”ⁱ In order to do that, ICER must effectively communicate information. However, the draft report not only has deviated from previous draft reports by being broken into two parts – with some important information shuttled into the “Supplemental Materials” part, with no apparent rationale for putting it there – but the “main” draft report contains some language that is confusingly complex, technical, and circular. For example:

- “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”ⁱⁱ We also note that Evidence Table 38 is on page 112 in the “Supplemental Materials” document and not in the main draft report.

- “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** (emphasis added).”ⁱⁱⁱ

Overall, the text of the draft report inappropriately assumes previous understanding of the underlying research and clinical nuances of treating anemia in people with CKD. Combined with the fact that writing itself is so convoluted, the report simply fails to communicate useful information or insights “to help stakeholders interpret and apply evidence to improve patient outcomes and control costs.”^{iv}

In addition, there are at least 17 bad hyperlinks in the draft report, including a link that appears to be intended to provide the list of stakeholders from whom ICER requested input for shaping the draft report.^v Attempting to make sense of the report was already challenging – without accurate links to the intended references, the attempt becomes absurd. Those bad links are indicative of sloppiness on the part of ICER, and its production team and management.

2. The draft report relies on questionable data sources

In past comment letters, we have noted that ICER relies much too heavily on data gathered before new treatments have been reviewed or approved by the FDA. But this draft report sets a new low standard for using limited, questionable data to make far-reaching conclusions. It appears that essentially all of the data used in the draft report’s “analyses” are from unpublished data. For example:

- “In the DI-CKD population, we identified four key **unpublished** Phase III RCTs of Roxadustat”^{vi} And “We identified four Phase III, multicenter RCTs of roxadustat in DI-CKD.17-20 All of the RCTs are currently **unpublished** (emphasis added)...”^{vii}
- “In the DD-CKD population, we also identified four key **unpublished** Phase III RCTs comparing roxadustat with ESAs”^{viii} And “We identified four Phase III, multicenter RCTs of roxadustat in DD-CKD. All RCTs are currently **unpublished** (emphasis added)...”^{ix}

3. The draft report demonstrates a weak understanding and poor presentation of the complexity of health care financing and Medicare reimbursements

In the past we have criticized ICER for not recognizing that different populations of people in the U.S. have very different types of insurance, which has implications not only for individuals’ costs, coverage and other access parameters, but also for projecting potential payer or system expenditures. Therefore, we were very glad to see that in the draft report ICER appeared to recognize this difference, and separated Medicare from commercial reimbursements.

Unfortunately, demonstrating a weak understanding of how Medicare works, ICER did not accurately present how this would actually work in the real Medicare reimbursement system. Roxadustat is an oral drug, and under general Medicare rules, medicines (such as oral drugs) that

people take themselves (i.e., are NOT administered by a physician) are covered under Medicare Part D, and are not part of the ESRD bundle payment or other reimbursement mechanism.

As noted in a January 2019 article in the *American Journal of Kidney Diseases*, “Medications that have no injectable equivalent, known as ‘oral-only medications,’ are currently excluded from the bundle and are paid separately through Medicare Part D.”^x While the oral medicine had previously been outside of the ESRD bundle payment, this article also discussed how the introduction of the first IV calcimimetic medicine triggered a transition payment for the oral and IV calcimimetics. Some may assume that this would mean that the introduction of an oral medicine for treating anemia in people with CKD would result in a similar action because injection treatments for anemia already exist within the bundle. However, under CMS’s current guidance, for the Transitional Drug Add-on Payment Adjustment (TDAPA) program add-on payments are only available for new injectable or intravenous drugs, which means that roxadustat, as an oral medicine, would not be eligible. (Note that CMS guidance clarifies that oral cinacalcet is an exception to that rule, and is covered under TDAPA: “While calcimimetics are included in the bone and mineral metabolism ESRD PPS functional category, they are an exception to the drug designation process as discussed in the Calendar Year (CY) 2016 ESRD PPS final rule (80 FR 69025, 69027).”)^{xi}

Second, even if roxadustat were to be considered for inclusion in the ESRD bundle, because it is used to treat anemia, it is unclear whether it would qualify for TDAPA because the program’s exclusion criteria includes: “New **injectable or intravenous** drugs or biologicals whose end action effect is the treatment or management of a condition or conditions associated with ESRD and for which there is an ESRD PPS functional category (emphasis added),” with “anemia management” being a specific ESRD functional category.^{xii} And thus, “The new injectable or intravenous product is considered included in the ESRD PPS bundled payment and no separate payment is available.”^{xiii} CMS has separately stated that “Only if a new drug also represents a new functional category would the proposed transitional drug add-on payment adjustment apply.”^{xiv}

And third, the provisions for inclusions and exclusions for Medicare’s transitional add-on payments also includes the requirements that the new drug be innovative and provide significant clinical improvement in that it “represents an advance that substantially improves, relative to technologies previously available, the diagnosis or treatment of Medicare beneficiaries.”^{xv}

Based on existing CMS guidance and long-standing practices, we assume that CMS’s intent is clear for not paying additional amounts for treatments that would be replacing other treatments that are already paid for within bundles (such as the ESRD PPS bundle payment), unless it can be shown that the new treatment would improve patient outcomes and would significantly increase costs for providers.

Overall, ICER’s presentation of the very complicated and nuanced mechanisms for Medicare reimbursements in the draft report is simply inadequate. ICER does not accurately capture how new treatments may be reimbursed in relation to bundled payments for ESRD, and the above cursory review of current CMS guidance and practice shows that the complexity of the situation does not merit ICER’s simplistic assumption that after FDA approval, roxadustat will be

January 4, 2021

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Dear Dr. Pearson,

The Partnership to Improve Patient Care (PIPC) appreciates this opportunity to comment on the Institute for Clinical and Economic Review's (ICER) draft evidence report regarding treatments for Anemia in Chronic Kidney Disease (CKD). Approximately 37 million Americans have kidney disease, with millions more at risk. The majority of individuals with kidney disease will experience anemia at some point in their disease progression.¹ Given this reality, it is important that effective treatments are made available to these patients. Please consider our below comments on how ICER may consider constructing its model to best serve these patients.

ICER's assessment is being conducted far too early without an appropriate amount of data. It is not clear why ICER has chosen to evaluate roxadustat as treatment of anemia in people with CKD at a time before the publication of the RCTs.

ICER's assessment is being conducted far too early, prior to even the publication of the randomized clinical trial (RCT) data for roxadustat. ICER identified four Phase III, multicenter RCTs of roxadustat in DI-CKD. All of the RCTs are currently unpublished, and data for this model was obtained from a clinical trial report,² a conference presentation,³ an investor presentation,⁴ and an unapproved Academy of Managed Care Pharmacy (AMCP) dossier.⁵

By using this premature data, ICER is developing a cost-effectiveness model that is utilizing incomplete datasets from unfinished RCTs. Data from incomplete trials would not be appropriate in the evaluation of effectiveness of a treatment, so we would argue that it is also not acceptable in measuring cost-effectiveness. We recommend ICER wait until publication of the RCT data prior to completing this model.

¹ National Kidney Foundation, 2020, <https://www.kidney.org/atoz/content/about-chronic-kidney-disease#facts>

² 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

³ 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.

⁴ 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>.

⁵ AstraZeneca. Roxadustat: AMCP Unapproved Product Dossier. 2020

ICER has developed a de novo model for evaluating treatment of anemia in people with CKD. There are previously published, more sensitive models, we would recommend using.

ICER's report describes the creation of a de novo decision-tree model that uses data from ongoing RCTs to estimate the relative effect of roxadustat as compared to the current standard of care of erythropoietin stimulating agents (ESA) for treating anemia in CKD. It does so by estimating the relative risk of having a major adverse cardiovascular event (MACE) or death from any cause when on each of the two treatments. The evaluation is split into two subgroups; patients with dialysis-independent (DI-CKD), and patients with dialysis-dependent CKD (DD-CKD).

We would recommend, instead of creating a de novo model for treating anemia in CKD, to look to already existing simulation models. In this case a strong model has already been published to evaluate these same outcomes.⁶ The previously published model is more complex, patient-centered, and capable of evaluating the questions of cost-effectiveness and value of treatments for anemia in CKD than the decision tree model described by ICER.

We recommend more focus on issues patients raised as important throughout the scoping process.

As our past comments to ICER have indicated, it is incredibly important to listen to the needs of the patient population in question and work to meaningfully incorporate their feedback into models. Our healthcare system should be focused on providing the best care to patients, so it is imperative we are measuring value based on the desired outcomes of patients, caregivers and clinicians.

Patients and advocacy groups roundly voiced a desire for more choices related to anemia management, particularly within the patient subpopulations 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. ICER should have heard these concerns and evaluated roxadustat in ESA-intolerant patients. There was no attempt made to evaluate roxadustat in ESA-intolerant patients, or in patients contra-indicated to ESAs.

Patients and clinicians also highlighted the importance of avoiding blood transfusion to decrease antibody formation and sensitization. This concern also appears not to have been addressed. The use of the previously mentioned model⁷ would have addressed this issue.

⁶ Yarnoff BO, Hoerger TJ, Simpson SA, Pavkov ME, Burrows NR, Shrestha SS, Williams DE, Zhuo X. The cost-effectiveness of anemia treatment for persons with chronic kidney disease. PloS one. 2016 Jul 12;11(7):e0157323.

⁷ Yarnoff BO, Hoerger TJ, Simpson SA, Pavkov ME, Burrows NR, Shrestha SS, Williams DE, Zhuo X. The cost-effectiveness of anemia treatment for persons with chronic kidney disease. PloS one. 2016 Jul 12;11(7):e0157323.

ICER has chosen to use outcomes that are not the primary or secondary outcomes of the trials.

ICER's model is based on the relative risk of either MACE or ACMR as primary or secondary outcomes. The RCTs that ICER's model is relying on are powered to measure changes in hemoglobin levels, as they are treatments for anemia. This means that they were not designed to measure MACE or ACMR, but to measure changes in hemoglobin levels, which is the primary purpose of the therapy being evaluated. As a result, the RCTs did not show statistically significant differences between the treatment and control arms in either patient group of interest for the primary and secondary outcomes in ICER's model, as these outcomes were not what the trials were designed to measure.

We would recommend using a model that is designed to measure hemoglobin levels, to align with the primary purpose of the therapy in question.

Conclusion

If ICER's goal is to provide decision makers with reliable, actionable data, then we would recommend it wait until enough high-quality data is available to conduct its assessments and ensure it is incorporating the desired outcomes of patients and primary purpose of the therapy in question. ICER's rushed studies, combined with the inherent flaws of quality-adjusted life years (QALYs), remain a significant concern for the patient and disability communities whose access to care is at stake. We continue to urge ICER to prioritize patients over payers in its work.

Sincerely,



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4 January 2021

**REF: TREATMENTS FOR ANEMIA IN CHRONIC KIDNEY DISEASE:
EFFECTIVENESS AND VALUE [Draft evidence Report]**

My dear Dr Pearson

I note, once again, that ICER, or more accurately the University of Washington model group, persists in creating imaginary lifetime simulations to support invented claims for pricing and product access ¹. Although I have advised that this approach to health technology assessment fails the standards of normal science, you persist in a methodology which is clearly pseudoscience in failing to develop credible, empirically evaluable and replicable claims ^{2 3 4 5 6}.

Of particular interest, in you belief in this meme, it the modeling of quality adjusted life years (QALYS). The QALY (or I-QALY) is a mathematically impossible construct as the multiattribute utility scores (in this case mainly based on the EQ-5D-3L) are ordinal scores ⁷. Previous efforts to elicit from you a coherent argument that the EQ-5D-3L is, indeed, a ratio scale have proved unrewarding. As you may be aware, a ratio scale (to support multiplication) requires a true zero. The EQ-5D-3L (and, for example, the HUI Mk3) does not have ratio properties as utilities can range from -0.59 to 1.0. This is recognized in the standard Drummond et al textbook (see pgs. 129-30) where it is pointed out that, indeed, the EQ-5D-3L does not have ratio properties ⁸. Unfortunately, the argument becomes confused where the claim is then made that the EQ-5D-3L has interval properties that can support multiplication. This is (i) incorrect given the axioms of fundamental measurement (the argument is confused) and (ii) no evidence is presented to show that the EQ-5D-3L actually has interval properties. This is not surprising as it was not designed to have those properties. The mistake made is to put ordinal scores on a number line with equal intervals and then assume the scores estimated from the EQ-5D-3L algorithm have interval properties.

Further, it is unclear that you are consistent in your use of EQ-5D-3L ordinal utilities (Table 4.2). You seem to be treating as equal the EQ-5D-3L, TTO and SF-36 utility algorithm. Perhaps I might remind you of a caution by Drummond et al (pg. 158) ⁸ in regard to which preference-based multiattribute system to use:

First, the decision does matter. These systems are far from identical. They differ in the population surveyed, in the dimensions of health they cover, in the number of levels defined on each dimension, in the description of those levels, and in the severity of the most severe level. In addition, they differ in the population surveyed and in the instruments used to determine the preference-based scoring. Finally they differ in the theoretical approach taken to modelling the preference data into a scoring formula.

As an example of an ordinal score from the ‘add-em up’ school of HRQoL claims, consider the Kidney Disease Quality of Life Short Form Questionnaire (KDQoL-SF) ⁹. This is comprised of 79 items, with 36 generic items (the SF-36) and an additional 45 kidney-disease specific questions. From the perspective of the axioms of fundamental measurement this is an absurd construct. First, it was not designed to have ratio let alone interval measurement properties (concepts that appear to be foreign to those ‘constructing’ the instrument). It is an ordinal score which cannot support the basic arithmetic operations. Second, it is multiattribute with scores for each of the multitude of attributes (generic and disease specific) added and transformed to a 0 to 100 scale. This is an ordinal scale which means we have no idea of the ‘distance’ between aggregate scores. Third, unlike the standards of measurement in the physical science, it does not focus on measuring single attributes relevant to patients with chronic kidney disease. It lacks construct validity (i.e., dimensional homogeneity). The aggregate overall score and scores on sub-domains such as the SF-36 are meaningless; there is no possibility of using this instrument to measure response to therapy or to compare patient groups. All you have are a collection of attributes which you add scores together without realizing that each attribute has its own dimensional character. This measure cannot support QALYs or any claims for QALYs (which, as noted, are an impossible construct anyway).

Given the I-QALY, claims made in this Washington CKD model are obviously of no account, your base case results (Table 4.4) where you claim no difference between the QALYs for roxadustat versus ESAs in the DI-CKD population are of no interest. They are constructs of your imaginary simulation, as are the other elements reported which are purely assumption driven. The same applies to the QALYs reported for the comparison with the DD-CKD population. Depending on the utilities selected, in any modeled simulation (and putting aside any reference to the axioms of fundamental measurement) means that if you change assumptions you change the results.

This last point brings me to your new cloud based platform, ICER Analytics ¹⁰. This seems an odd endeavor as, with access to your backbone model, users (should they feel inclined) can modify assumptions on timeframe, costs, utilities, et. This allows the re-invention of cost-per-I-QALY and threshold pricing that may (indeed, by design) contradict your modeling. This illustrates the empty nature of simulation modeling as a guide to formulary decision making. Presumably, if challenged, this would put ICER and the opposition in the position of having to

defend modeled assumptions. This would made more interesting as your assumptions are for an imaginary world stretching 30 years of more over the lifetimes of a hypothetical population. Perhaps you might care to comment? When you post this Washington CKD model to ICER Analytics, it will be interesting to see how sensitive your model claims are to varying key assumptions (e.g., alternative utility scores).

It is not, of course, a question of ‘modifying’ utilities but of rejecting them as having no role in formulary decisions. The focus must be on evaluating single attributes, whether these refer to clinical, quality of life or resource utilization claims as detailed in the recently released Version 3.0 of the Minnesota formulary submission guidelines that meet the standards of normal science¹¹.

The identical utility scores (Tables 4.4 and 4.5) should come as no surprise as they reflect your choice of assumptions. The EQ-5D-3L and other multiattribute utility scores virtually ensure that your lifetime utilities will be very close. This is because with the limited symptoms or attributes captured (in the EQ-5D-3L five symptoms: mobility, self-care, usual activities, pain/discomfort and anxiety/depression with three response levels: (no problem, some problem, extreme problems). only one or two will be relevant to the disease state. The ‘no problem’ or zero weight attributes will dominate as shown by the scoring algorithm . Perhaps you might have addressed the question of whether or not patients and caregivers believed that their needs were better met with Roxadustat than the comparator(s). But, of course, you cannot address this question with an instrument that fails to meet fundamental measurement standards.

Given the ‘change the assumptions’ driven marketing case for ICER Analytics, it might be appropriate to point out that your claims (or any future claim) driven by assumption (the invented claims) fail the test of logic; specifically, Hume’s problem of induction. Simply, not all swans are white. ICER Analytics’ curated model claims for ‘fair’ prices, created by application of I-QALY thresholds, are never ‘wrong’. Driven by assumption it fails the simple proposition that it cannot be *‘established by logical argument, since from the fact that all past futures have resembled past pasts, it does not follow that all future futures will resemble future pasts’*¹² Certainly, assumptions may be critical to model empirically evaluable claims; the difference is that the claims are falsifiable and a failure leads us to reconsider the model structure and its assumptions.

But, of course, your business case demands a modelled claim even through as pointed out in the draft evidence report you have insufficient evidence to make any meaningful clinical comparisons, let alone evidence for the choice of assumptions driving the model (to include consistent ordinal utility claims). Claims from assumptions (apart from their logical absurdity) means that there can be no claim for ‘superiority’ from one variant of your backbone ICER Analytics modifiable model over another. Indeed, you make it more obvious as there is a common core unlike different models for CKD found in the literature.

If formulary decision making is focused on the utilization of dispersed knowledge then the economic problem, as Hayek eloquently put it in his 1945 seminal essay, is how to secure the best use of that knowledge that is not given to anyone in its totality¹³. The problem with the ICER creation of imaginary information, in the invention through an assumption driven

simulation of non-evaluable claims for pricing and access or rationing of products, is to subvert the process by which information is created and utilized, and markets function. To paraphrase Hayek: every time market exchange is restricted, ignorance is substituted for knowledge.

I have no doubt that ICER will continue to insist that multiattribute utility scores are ratio scales. You have no option as it is central not only to your 'fair pricing' claims but to your business case with ICER Analytics. I imagine we can look forward to many competing 'fair pricing' claims to support manufacturer's pricing strategies across disease areas. You are really spoiling us.

All the best for the New Year

Yours sincerely

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“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]).”^{xvi}

4. The draft report’s conclusions are bad

Because of those bad aspects of the draft report noted above, the quantitative conclusions ICER presents in the draft report are suspect, problematic, and highly questionable. Therefore, we urge ICER to go back and correct its research and analytical mistakes and reissue a draft report, rather than proceeding to issuing a final report using this inaccurate, inappropriate, and misleading approach.

People-Centered Perspectives

Chronic kidney disease (CKD) is a significant health problem in the U.S. that is often caused by diabetes or high blood pressure. People with CKD can also face restricted care options for other diseases because limited kidney function may complicate or preclude the use of certain treatments or diagnostic tests. And certainly, when a person requires dialysis because their kidneys are no longer functioning adequately, his or her life changes dramatically.

Within the scope of the draft report, we agree that having an oral option for treating anemia in people with CKD is a good thing because it gives them and their care team an additional option. As we and many others have noted, having multiple options for treating complex medical conditions is a good thing for patient care, patient quality of life, and society overall.

Similarly, oral treatments can simplify care for people with CKD by reducing their need to visit medical providers, which could reduce time away from work or family, as well as reduce difficulty in accessing treatment. As the draft report notes, “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.”^{xvii}

We appreciate ICER looking into one aspect of the complicated landscape of treatment and care coordination confronting someone with significant or end-stage renal disease as they work with their care team to replace the toxin clearing, water managing, electrolyte balancing, and hormonal functions of the kidney with medical interventions. We point this out since anemia of CKD – which is the sole focus of the draft report – is only one aspect of CKD that patients need to monitor and manage with their care team, which is often a large group of clinicians with specialized skills and expertise. And as the draft report notes, improving anemia may provide individuals with CKD relief from symptoms like fatigue, which can significantly improve quality of life (QoL) – although, unfortunately, data on this matter seems to be limited. We would hope that ICER would encourage researchers to pursue more robust evidence of QoL in their future work. However, we are also disappointed that ICER decided to de-emphasize even the limited QoL data by relegating it to the “Supplemental Materials” document.^{xviii}

Uncertainties and Assumptions

The draft report cites unpublished data as the sources for its analyses, but does not recognize that roxadustat has been approved for use in Japan – other than a passing reference to potential harms.^{xix} The draft report should fully discuss the approval in Japan, and other relevant

information from that regulatory action – or justify why such information is not applicable to ICER’s evaluation of roxadustat.

One assumption in particular from the draft report exemplifies the troubling amount of uncertainty in this draft report: “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.”^{xx} However, the draft report also states 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.”^{xxi} This assertion implies that the evidence for this relates to people with CKD, but we note that one of the sources cited for that statement (reference #11) is from a study of treating anemia in people with cancer. We agree that this issue is important, and as such ICER should be very, very careful in its analyses and in presenting any calculations or conclusions from the draft report, or in a final report.

Additional Point

- The draft report repeatedly uses the terms “incident” and “stable” related to dialysis, but the draft report does not define those terms. ICER should define those terms since “incident” in particular seems to have several different technical definitions in the research literature.

Conclusions

Patients Rising Now agrees with the regulatory authorities in Japan that “roxadustat has efficacy in the treatment of renal anemia, and that roxadustat has acceptable safety in view of its benefits.”^{xxii} We think that ICER’s draft report reaches a similar conclusion, but because of the tangled writing and convoluted analyses, we are not certain. Therefore, we also urge ICER to take time to produce a more clearly written document for consumption by the public stakeholders that ICER states are its intended audience, as well as for its own review committee.

Overall, we are very concerned that ICER’s badly constructed and written draft report contains analyses based on undocumented and unpublished data, which leads to misleading conclusions. And because of that, should others rely on ICER’s “findings,” we are concerned that care for people with anemia due to CKD will be impaired and their quality of life reduced.

Sincerely,



Terry Wilcox
Co-Founder & Executive Director, Patients Rising Now

ⁱ Draft report, p ii
ⁱⁱ Draft report, p 14
ⁱⁱⁱ Draft report, p 21
^{iv} Draft report, p ii
^v Draft report, p iii

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- ^{vi} Draft report, p ES2
- ^{vii} Draft report, p 5
- ^{viii} Draft report, p ES2
- ^{ix} Draft report, p 6
- ^x [https://www.ajkd.org/article/S0272-6386\(18\)31124-7/fulltext](https://www.ajkd.org/article/S0272-6386(18)31124-7/fulltext)
- ^{xi} CMS Guidance Document “Implementation of the Transitional Drug Add-On Payment Adjustment,” MM10065, January 1, 2018.
- ^{xii} <https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ESRDpayment/ESRD-Transitional-Drug>
- ^{xiii} <https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ESRDpayment/ESRD-Transitional-Drug>
- ^{xiv} 80 FR 68967, Medicare Program; End-Stage Renal Disease Prospective Payment System, and Quality Incentive Program, 11/6/2015
- ^{xv} C.F.R. Title 42, Chapter IV, Subchapter B, Part 412, Subpart F, §412.87 https://www.ecfr.gov/cgi-bin/text-idx?SID=907085a13146c586c6615cd4a9c3f2b5&mc=true&node=se42.2.412_187&rgn=div8
- ^{xvi} Draft report, p 23
- ^{xvii} Draft report p 30
- ^{xviii} Supplemental Materials document, pp 29-30 and pp 38-39
- ^{xix} Draft report, p 12
- ^{xx} Draft report, p 14-15
- ^{xxi} Draft report, p 2
- ^{xxii} Report on the Deliberation Results for Roxadustat, Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Japan’s Ministry of Health, Labour and Welfare, September 4, 2019, p 84