Anemia in Chronic Kidney Disease
Response to Public Comments on Draft Evidence Report

January 28, 2021

Table of Contents

#	Comment	ICER Response
Manufacturers		
Amgen		
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)… 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.	The scope of the economic analysis is aimed to quantify the cost and health outcomes of roxadustat compared with current standard of care, using available data at the time of analysis. The economic model was designed to incorporate the full cost of CKD, in alignment with good modeling practices to consider all health effects and costs relevant to the decision problem. As stated, in this specific case in the DD-CKD population, a lower total cost result is seen in patients treated with roxadustat, driven in part due to the potential increase in mortality. Care was taken in the draft Evidence Report to emphasize that this lower cost was coupled with worse health outcomes in these scenarios. However, in other scenarios, there is also a reduction in cost attributable to reduced utilization of IV iron and red blood cell transfusions. We have revised page ES2 to articulate this point more clearly.
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." 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	As noted, the degree of uncertainty is clearly shown in the probabilistic sensitivity analysis. To further reinforce the uncertainty of our findings, 95% credible interval results from the probabilistic sensitivity analysis have been added to the Executive Summary.

#	Comment	ICER Response
	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.	
3.	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 evidence, 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. 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.	We agree with this suggestion that interpretation of the results based on point estimates alone does not provide the reader with a complete picture for which to understand the uncertainty surrounding the results of the economic evaluation. We edited our report to include uncertainty intervals for key findings and displayed supporting uncertainty findings within the Report Supplement.
4.	Incorporate the FDA label and the KDIGO recommendations for ESA in the roxadustat budget impact analysis. ICER uses definitions of anemia (Stauffer and Fan, 2014) that conflict with the current Kidney Disease Improving Global Outcomes (KDIGO) 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) 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. divides anemia by Hb cutoffs	We added the following language to our report to defend our approach of evidence in the BIM population estimates: "We used epidemiology evidence to estimate the US population with anemia for CKD stages III through V. We note that given the safety profile of currently-available treatments including ESAs, the population that is currently taking ESAs and may consider roxadustat, if available, is a subset of those with anemia and CKD. To account for this difference between an anemia with CKD population and the subset currently taking ESAs, we assumed 50% of those who self-reported as having anemia treatment were taking ESAs and may be eligible for roxadustat. Other approaches to estimate the number of patients taking ESAs for CKD include following KDIGO recommendations and may lead to lower estimates of a roxadustat eligible population when comparing to those currently taking ESAs. Given the emerging safety evidence for roxadustat, we first characterized the broader population approach of

#	Comment	ICER Response
	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 … 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.	anemia for CKD stages III through V. This characterization allows for the flexibility of evaluating future treatments of anemia for CKD with varying safety profiles."
GlaxoSmithKline		
1.	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. 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 hemoglobin.	Our evaluation is informed by the available evidence, and we acknowledge the limitations of using inflammation status as a surrogate for hyporesponsiveness. Manufacturers should design trials and report results that better explore this issue.
2.	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 and active-controlled 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.	We acknowledge the differences in the use of rescue therapy between the treatment arms in the trials; however, we are limited by the available data and not able to further explore the impact of these differences and the direction of the bias this may lead to. We have added language in our report to describe this as an area of uncertainty.
AstraZeneca and FibroGen		
1.	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	Given the evidence available at the time of analysis and the "I (insufficient)" rating, we chose to report the results of the economic analysis using a cost-consequence framework rather than the more typical cost-per-QALY gained. In addition, we explored several different reimbursement scenarios in the commercial and Medicare settings. This analysis will be updated if, prior to publication of the final Evidence Report, the full publication of the roxadustat Phase III results becomes available or an FDA decision occurs.

#	Comment	ICER Response
	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.	
2.	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 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). 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 appreciate this comment. We have removed our meta-analysis of all-cause mortality in the DI-CKD population from the revised Evidence Report and Supplement. However, it should be noted that the point estimate from the pooled analysis of the intent-to-treat DI-CKD population (HR: 1.06; 95% CI: 0.91 to 1.23) is in the same direction as the point estimate from our previous meta-analysis (HR: 1.15; 95% CI: 1.00 to 1.33) and includes potentially large benefit and harm given the high baseline risk of mortality in this population. The individual RCT data used to create the meta-analysis were abstracted from the pre-approval AMCP dossier and clinicaltrials.gov, as cited in the draft Evidence Report. Specifically, the data can be found at the following locations in the dossier: • ALPS: Page 46 • ANDES: Page 44 • OLYMPUS: Page 47

#	Comment	ICER Response
3.	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. 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, 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.	We made the decision to include the results from the PYRENEES trial in the pooled safety and efficacy analyses because ESAs have been shown to have similar efficacy and safety profiles. (*Please see Palmer S, et al. Erythropoiesis-stimulating agents for anaemia in adults with chronic kidney disease: a network meta-analysis*.) We have reviewed the concerns about potential differences in these trials, but we do not see any evidence or have data to support such differences. As such, based on the available evidence on these studies, we believe results from PYRENEES should be included in the pooled safety and efficacy analyses of the DD-CKD population.
4.	Furthermore, the proposed analyses do not explore the cost-effectiveness of roxadustat in the subgroup of patients with incident dialysis, where a larger	The overall DD-CKD population can be divided into two subpopulations: incident dialysis (a pre-specified subgroup) and stable dialysis. The decision to

#	Comment	ICER Response
	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.	separately evaluate subgroups is based on a complete review of the available data to determine if there is a true subgroup effect. ICER has requested additional data from the manufacturer to understand efficacy and safety outcomes of roxadustat more fully in **both** subpopulations. To date, only information pertaining to the incident-dialysis subpopulation is available to us. The observation that a larger reduction in MACE was observed in the incident-dialysis population compared with the overall DD population means conversely that a smaller reduction in MACE must be observed in the stable dialysis population. For this reason, we have not emphasized results in the incident-dialysis subpopulation without presenting a balanced interpretation of the results in the stable subpopulation.
5.	Medicare will issue guidance on eligibility and reimbursement for roxadustat via the TDAPA payment system in 2021… 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.	The specific extent and timing of inclusion of roxadustat into a bundled payment system or details of the reimbursement under TDAPA remain uncertain. In addition, innovative payment systems may not apply to the DI-CKD population. For this reason, we explored several different reimbursement scenarios in the commercial and Medicare setting. In the report, we presented two primary scenarios. One of these scenarios is that roxadustat would be included into the bundled payment system after three years based on prior TDAPA experiences, incurring no additional cost relative to ESAs. In a commercial payer scenario, we assume the drug acquisition cost of ESAs was derived from ASP pricing outside of a bundled payment. This later scenario provides a comparison that includes the drug-acquisition cost of ESA explicitly.
6.	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	As stated in a prior response, the economic model was designed to incorporate the full cost of CKD. In alignment with good modeling practices, we considered all health effects and costs related to the treatment and relevant to the decision problem. The approach is intended to be comprehensive and

#	Comment	ICER Response
	analysis. 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.	independent of the interpretation of any one resulting output of the model.
7.	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. 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. Further, following a kidney transplant, patients with history of RBC transfusions have a higher risk of kidney rejection due to alloimmunization. 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.	The model includes the direct cost and QALY decrement associated with IV iron and red blood cell transfusions as well as the impact of roxadustat versus ESAs on these outcomes. We agree that there are potentially important consequences of red blood cell transfusions related to transplant that are not fully captured within the model because of the difficulty in quantifying these outcomes. As such, we revised the report to include this as a limitation of the economic model.
8.	We would like to note the following transcription errors in the report. • 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	Thank you. Regarding the first two points, we have corrected these errors in the revised Evidence Report and Supplement. Our response to the last point is described above.

#	Comment	ICER Response
	period, and adjusting for time-at-risk by treatment group.	
Pfizer		
9.	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 20201. 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. 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 highlighting pricing dynamics within the ESAs, including biosimilars. Consistent with ICER's Value Assessment Framework Section 3.8, "ICER's cost-effectiveness analyses will not routinely make estimates of price changes across comparator treatments linked to patent and exclusivity time horizons." We added text to the Uncertainties and Controversies section of the report mentioning the uncertainty about future ESA pricing.
Patients/Patient Groups		
Patients Rising Now		
1.	The draft report is poorly written, badly organized, and sloppy. ICER's stated goal is to "to help stakeholders interpret and apply evidence." 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	As ever, we very much appreciate input from Patients Rising Now on how we can best write and communicate within our reports. As discussed below, a technical issue interfered with the hyperlinks in the report, making the intended split of materials ineffective for users. We will be continuing to refine these split reports as we work through the next few

#	Comment	ICER Response
	"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. 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."	ICER reports and receive valuable feedback from our readers such as Patient's Rising Now.
2.	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. 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.	Thank you for your comment. After publication of the draft Evidence Report, our website was overhauled, which altered hyperlink destinations. All hyperlinks in the revised Evidence Report are correct.
3.	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" And "We identified four Phase III, multicenter RCTs of roxadustat in DI-CKD.17-20 All of the RCTs are currently **unpublished** (emphasis added)…" • "In the DD-CKD population, we also identified four key **unpublished** Phase III RCTs comparing roxadustat with ESAs" And "We identified four Phase III, multicenter RCTs of roxadustat in DD-CKD. All RCTs are currently **unpublished** (emphasis added)…"	We recognize that data are often limited for new treatments. However, patients, clinicians, and insurers continue to be faced with decisions about how to best use these treatments once they are approved for use. Thus, we view comparative effectiveness research and economic modeling as important ways to identify key inputs that impact the effectiveness and cost of a new treatment. Our report highlights the limitations of these data as well. Further, since our initial literature search, data from a key RCT in the DI-CKD population, ANDES, and a pooled analysis of the incident-dialysis subgroups of three key RCTs, HIMALAYAS, ROCKIES, and SIERRAS, have been published electronically. (*Please see Coyne DW, et al. Roxadustat for Chronic Kidney Disease-related Anemia in Non-dialysis Patients and Provenzano R, et al. Pooled Analysis of Roxadustat for Anemia in Patients with Kidney Failure Incident to Dialysis.*) These data have been incorporated into our revised Evidence Report and Supplement.

#	Comment	ICER Response
4.	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.	We very much appreciate that Patients Rising Now is apparently clear on how reimbursement of roxadustat will occur under Medicare, despite that understanding conflicting with what the manufacturer believes will occur.
5.	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.	We agree that data on HRQoL are limited, and our final Evidence Report will highlight this evidence gap. HRQoL is discussed in the report on pages 8-9 for the DI-CKD population, on pages 10-11 for the DD-CKD population, and on page 13 for the subgroup of the DI-CKD population defined by inflammation state.

#	Comment	ICER Response
6.	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. 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.	An approval is not evidence.
7.	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." 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." 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.	The sentence does not specifically talk about anemia in CKD and hence the references including number 11 in cancer patients are appropriate. However, to avoid any confusion and due to the abundance of evidence in patients with CKD, we will delete reference 11.
8.	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.	Thank you. We have defined these terms in our revised Evidence Report and Supplement.
PIPC		
1.	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, a conference presentation, an investor presentation, and an	We recognize that data are often limited for new treatments. However, patients, clinicians, and insurers are still faced with decisions about how to best use these treatments once they are approved for use. Thus, we view comparative effectiveness research and economic modeling as important ways to identify key inputs that impact the effectiveness and cost of a new

#	Comment	ICER Response
	unapproved Academy of Managed Care Pharmacy (AMCP) dossier. 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.	treatment. Our report highlights the limitations of these data as well. Further, since our initial literature search, data from a key RCT in the DI-CKD population, ANDES, and a pooled analysis of the incident DD-CKD subgroups of three key RCTs, HIMALAYAS, ROCKIES, and SIERRAS, have been published electronically. (*Please see Coyne DW, et al. Roxadustat for Chronic Kidney Disease-related Anemia in Non-dialysis Patients and Provenzano R, et al. Pooled Analysis of Roxadustat for Anemia in Patients with Kidney Failure Incident to Dialysis.*) These data have been incorporated into our revised Evidence Report and Supplement.
2.	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. 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.	We heard these concerns and documented them in our report on page 3. We also agree decisions should be patient-centered and based on the effects on patient important outcomes. Data regarding roxadustat specifically in ESA-intolerant patients or those who have a contraindication to ESAs were not available. However, these are important subgroups to be considered in clinical decision-making. For that reason, on page 16 of the report, under the summary of roxadustat compared to usual care group, we state, "We feel that in such patients where ESAs are not available, roxadustat would likely provide a net clinical benefit despite the potential for harms."
3.	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 model would have addressed this issue.	We are familiar with the CKD Health Policy Model, adapted to the treatment of anemia in CKD by Yarnoff and colleagues. This model does provide a more granular approach to modeling anemia in CKD. However, clinical trial data for roxadustat is not available to us with sufficient granularity to inform the inputs for this model structure. In addition, development of a *de novo* model allowed for modeling of mortality and MACE+ by treatment arm from the roxadustat trials rather than by hemoglobin level. Notably, the model adaptation by Yarnoff et al. also does not directly consider the consequences of antibody formation and/or sensitization resulting from

#	Comment	ICER Response
		red blood cell transfusions, nor do any other published models that we are aware of. We have included a statement on this limitation in the revised Evidence Report.
4.	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 measures 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.	Decisions about whether to use a treatment option should be based on its effects on important outcomes to patients like mortality and cardiovascular events and not on surrogate outcomes like hemoglobin. As we state in our report, "despite the association between anemia and higher mortality in uncontrolled studies, subsequent evidence based on RCTs emerged and showed that correction of anemia and maintenance of hemoglobin to near normal levels with ESAs increased mortality and cardiovascular events without consistently improving quality of life." For that reason, we will include the outcomes that matter to patients and not just those that are easily measured in trials. We would hope that patient-focused organizations would support a focus on patient-important outcomes.
Economists		
Paul Langley		
1.	Of particular interest, in your 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. 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. 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.	We (and most health economists) have the understanding that changes in the EQ-5D (and other multi-attribute utility instruments) do have ratio properties. The EQ-5D value sets are based on time trade-off assessments (which are interval level), with preference weights assigned to different attributes. We fail to see why this should be considered as an ordinal (ranked) scale. The dead state represents a natural zero point on a scale of health-related quality of life. Negative utility values on the EQ-5D scale represent states considered worse than dead.

#	Comment	ICER Response
	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.	
2.	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.	We agree that the results are dependent on the set of inputs and assumptions used within the economic model, and changes to these assumptions changes the results. As with any model, we are dependent on the data available to us to provide inputs into the model. The primary purpose of sensitivity analysis is to explore to what degree changing inputs and assumptions within reasonable bounds driven by levels of parameter uncertainty (e.g., confidence intervals) changes the result.
3.	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.	As demonstrated by Table F1 in the Supplement, the absolute QALY shortfall ranges from below 1.0 to over 40.0 QALYs across a sample of disease states that ICER has recently evaluated. Therefore, potential cures within this sample of diseases would suggest wide-ranging differences in QALYs gained. We share an appreciation for logical thought processes and the search for truth. We highlight that roxadustat's inability to positively move a measure like incremental QALYs is consistent with our "insufficient" evidence rating from the comparative effectiveness review. To attempt to attribute this inability to the measure and not the treatment fails to meet logical thought processes. ICER and other cost-effectiveness researchers have shown wide-ranging incremental QALYs across the sample of treatments evaluated. Finally, Section 5 of the report includes a discussion on potential impacts of the treatment on patients, caregivers, and family.