SUMMARY OVERVIEW

Amgen appreciates the opportunity to comment on ICER's *Draft Background and Scoping Document for the Assessment of Clinical Effectiveness and Value of Treatments for Anemia in Chronic Kidney Disease (CKD).* It is estimated that at least 6% of the adult population in the US suffers from stage one and two CKD with an additional 4.5% of the US population in stages three and four.[1] Anemia is common in patients with CKD with it being observed as early as stage three. Anemia is almost universal by stage four, where the primary cause is insufficient production of erythropoietin by the diseased kidneys,[2] with many patients requiring treatment with erythropoiesis-stimulating agents (ESAs).

Amgen as a science-based company is committed to building a foundation of quality treatments and future advancements for anemic CKD patients in the areas of new medicine. As the manufacturer of Aranesp® and Epogen®, proven treatments for anemia caused by CKD disease both among patients on dialysis and those not on dialysis, Amgen has 30 years of experience in this area and are intimately familiar with the nuances that ICER could face in this assessment. We appreciate that ICER continues to take steps to incorporate elements that are important to patients and reflective of real-world clinical practice and highlight in this letter, a few important considerations for ICER:

1. **Population:** Aranesp® and Epogen® should not be evaluated in pre-dialysis (dialysis independent (DI)-CKD) patients because these drugs account for only 10% of all erythropoietin-stimulating agent (ESA) use in this patient population.
2. **Comparator:** The comparator should be reflective of the standard of care used in the dialysis dependent (DD-CKD) population in the clinical trials for roxadustat.
3. **Unique payment for dialysis:** This analysis should capture how each product is paid for in the real world. Roxadustat, as a new intervention, will be paid for separately; this is opposed to the payment structure for ESAs, which are a part of the standard of care guidelines and are a capitated Medicare payment for dialysis services.
4. **Perspective for cost inclusion:** When using the healthcare system/payer perspective, the payer should be defined as Medicare for dialysis patients.

Amgen is pleased to collaborate to inform a balanced, science-based assessment that builds on the existing knowledge base and ensures the needs of patients are addressed. Our comments are further detailed below:

KEY RECOMMENDATIONS

1. Population: Aranesp® and Epogen® should not be evaluated in pre-dialysis patients as these only account for 10% of all pre-dialysis use.

Procrit® and Mircera® together account for approximately 90% of ESA use in pre-dialysis (DI-CKD) patients. As of December 2019, Epoetin alfa use for DI-CKD was less than 20%.[3] The majority of pre-dialysis erythropoiesis stimulating agent (ESA) use is held by Janssen/ J&J for Procrit. When one applies a defined daily dose summary of use by product and the most recently published average selling price (ASP), Amgen ESAs account for approximately 10% of this total; Procrit and Mircera account for

the remainder in nephrology clinics. Therefore, Aranesp and Epogen should not be included in this patient population evaluation because both agents are rarely used in pre-dialysis. This modification will make ICER's analysis more reflective of clinical practice for these patients.

2. **Comparator: The comparator should be reflective of the standard of care used in the clinical trials for roxadustat for the dialysis dependent population.**

Roxadustat's comparator in dialysis (DD-CKD) should be reflective of clinical practice, which includes an ESA for the majority of patients. ICER's draft scoping document outlines a comparator as '*usual care (estimated by placebo arms of clinical trials*)',[4] however, roxadustat's ROCKIES, SIERRAS, and HIMALAYAS phase 3 pivotal trials in dialysis patients[5,6,7,8] applied an active ESA comparator, epoetin alfa. Therefore, ICER's comparator should be a weighted average ESA. The KDIGO clinical practice guidelines recommend ESAs when hemoglobin concentration falls below <10g/dL in adults, young people and children aged 2 years and older.[9] The dialysis Outcomes and Practice Patterns Study (DOPPS) as of February 2020, reports that 85.5% anemic patients received an ESA.[10]

3. **Unique payment for dialysis: This analysis should capture how each product is paid for in the real world. Roxadustat, as a new intervention, will be paid for separately; this is opposed to the payment structure of ESAs, which are a part of the standard of care guidelines and are a capitated Medicare payment for dialysis services.**

Unlike ESAs, roxadustat will not be part of the bundled payment for which the majority of ESAs for dialysis patients are paid. ICER has acknowledged the unique payment arrangements of dialysis patients. All dialysis services are bundled into the Medicare End Stage Renal Disease (ESRD) Prospective Payment System (PPS)[11] and this includes payments to cover lab tests, supplies and medications including the costs of ESAs for each dialysis treatment.[12] In contrast, roxadustat will initially be paid separately, either through Part D of Medicare or through the Transitional Drug Add-on Payment Adjustment (TDAPA). The Medicare ESRD PPS dialysis bundled payment includes the cost of an ESA, even when an ESA is not used. Therefore, Medicare will incur additional costs when roxadustat is used by dialysis patients beyond those contained in the dialysis capitated payment (which already includes the cost of an ESA and does not dictate/distinguish between specific ESAs for the payer perspective). Moreover, patients may see an additional co-payment for roxadustat over the services that they receive as part of dialysis, which means that they also will be effectively paying for this treatment twice (with the ESA in the bundled payment and for roxadustat). For this reason, it will be hard to compare roxadustat with ESAs.

4. **Perspective for cost inclusion: When using the healthcare system/payer perspective, the payer should be defined as Medicare for dialysis patients.**

Medicare pays for the majority of dialysis patients and so in any cost-effectiveness evaluation, the payer perspective should be Medicare. ICER has indicated that they are likely to use the societal perspective as part of the co-base case, which will also include the healthcare system/payer perspective. We recommend a more specific definition of the payer perspective. Most dialysis patients are paid for under Medicare including those under 65 years of age.[13] In the most recently available *Annual Data*

Report (2018) from the U.S. Renal Data System, 80% of patients are paid for by Medicare.[14] In adhering to common best practices in health technology assessment and cost-effectiveness analysis reflected in the U.S. *Second Panel on Cost-effectiveness in Health and Medicine*,[15] in adopting the payer perspective, ICER should only reflect those costs that Medicare – the payer - incurs.[16,17]

As ICER evaluates the weighted average ESAs in dialysis from the payer perspective, there should be no additional cost for these drugs above the bundled payment. This is the most accurate representation of the actual cost that Medicare incurs, as follows and outlined in Table 1 below:

- *For roxadustat*, this is the bundled payment plus the roxadustat wholesale acquisition cost (WAC): this WAC will represent the TDAPA CMS adds to the bundled payment until the ASP is established.
- *For the weighted average ESAs*, this is only the bundled payment: separate inclusion of the price of an ESA would result in double counting the payment for ESAs, which are already paid as part of Medicare's ESA payment within the ESRD PPS.

Table 1: Cost inclusion when taking the Medicare perspective

Drug Costs		ESRD Bundled Payment (includes ESA)
roxadustat	ESAs	Medicare End Stage Renal Disease (ESRD) Prospective Payment System (PPS) CY 2020 Base Rate[18]
WAC	$0*	$240

*Aranesp and Epogen are already included in the Medicare End Stage Renal Disease (ESRD) Prospective Payment System bundled based rate, so should not be added separately.

We also encourage ICER to refer to the various stages of CKD as defined over the last decade by the National Kidney Foundation through the KDOQI[19] and KDIGO[20] processes. This aimed to standardize terminology for the broad nephrology community to avoid confusion.

CONCLUSION

It is important that ICER's assessment recognize the inherent complexities in the payment of dialysis services given a bundled payment structure: in defining the payer perspective (with the societal perspective co-base case), ICER should use the perspective of Medicare, not commercial payers. Equally, ICER should only include Aranesp and Epogen in ICER's evaluation of dialysis patients, given the limited use of these products in pre-dialysis patients. Notably, ICER should also recognize that there are limitations to this analysis in informing patient access or policy, because the bundled reimbursement dynamics for ESAs versus roxadustat's TDAPA or oral-only status are key drivers in this assessment.

REFERENCES

[1] Jameson JL, Kasper DL, Longo DL, Fauci AS, Hauser SL, Loscalzo J. Harrison's Principles of Internal Medicine. 20th-ed. New York: McGraw-Hill Education; 2018. 305, Chronic Kidney Disease; p. 2113-2118.
[2] *Op. Cit.* Jameson *et al.* 2019.
[3] Jefferies. Equity Research: AstraZeneca PLC. Dec 2019; 20-22.
[4] ICER. Treatments for Anemia in Chronic Kidney Disease. Draft Background and Scope. July 20, 2020. p. 4. Link
[5] Evaluation of Efficacy and Safety of Roxadustat in the Treatment of Anemia in Stable Dialysis Subjects. ClinicalTrials.gov. Link
[6] Safety and Efficacy Study of Roxadustat to Treat Anemia in Patients with Chronic Kidney Disease, on Dialysis. ClinicalTrials.gov. Link
[7] Safety and Efficacy Study for Treatment of Anemia in ESRD Newly Initiated Dialysis Patients (HIMALAYAS). ClinicalTrials.gov. Link
[8] Inserro A. Data From 3 Roxadustat Trials Lead Off Kidney Week Sessions Ahead of Efficacy, Safety News. Kidney Week 2019. AJMC. November 08, 2019. Link
[9] KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. Kidney International Supplements: KDIGO. Official Journal of the International Society of Nephrology. 2012; Vol 2 (4). Link
[10] DOPPS Practice Monitor. DOPPS. Feb 2020. Link
[11] Section 1881(b)(14) of the Social Security Act requires a bundled PPS for renal dialysis services furnished to Medicare beneficiaries for the treatment of ESRD effective January 1, 2011. Link
[12] ESRD PPS Transitional Drug Add-on Payment Adjustment. CMS.gov: Centers for Medicare & Medicaid Services. March 2020. Link
[13] CMS. End-Stage Renal Disease (ESRD). Link
[14] United States Renal Data System. Chapter 9: Healthcare Expenditures for Persons with ESRD. Figure 9.3. Link
[15] Sanders GD, Neumann PJ, Basu A, Brock DW, Feeny D, Krahn M, Kuntz KM, Meltzer DO, Owens DK, Prosser LA, Salomon JA. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: Second Panel on Cost-effectiveness in Health and Medicine. JAMA. 2016 Sep 13;316(10):1093-103.
[16] CMS. End-Stage Renal Disease (ESRD). Link
[17] United States Renal Data System. Chapter 9: Healthcare Expenditures for Persons with ESRD. Figure 9.3. Link
[18] Section 1881(b)(14) of the Social Security Act requires a bundled PPS for renal dialysis services furnished to Medicare beneficiaries for the treatment of ESRD effective January 1, 2011. Link
[19] KDOQI: Kidney Disease Outcomes Quality Initiative.
[20] Levey AS, Eckardt K, Dorman NM, Cheung M, Jadoul M, Winkelmayer WC. Nomenclaure for kidney function and disease: report of a Kidney Disease: Improving Global Outcomes (KDIGO) Consensus Conference. Kidney International. 2020; 97: 1117-1129. Link

August 7, 2020

Dr. Steven D. Pearson
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Re: ICER evidence review of treatments for anemia in chronic kidney disease (CKD)

Dear Dr. Pearson,

AstraZeneca and FibroGen appreciate the opportunity to comment on the draft scoping document for the assessment of roxadustat. Roxadustat is an oral, first in a new class of drugs known as hypoxia-inducible-factor prolyl hydroxylase (HIF-PH) inhibitors and is currently under FDA review for the treatment of dialysis dependent (DD) and non-dialysis dependent (NDD) patients with anemia of CKD.

Roxadustat is poised to offer a major innovative physiologic approach for the treatment of patients with anemia of CKD in an area that has seen little advancement in well over three decades.[1] Compared to current therapies, roxadustat mimics the body's natural response to low levels of oxygen. Roxadustat activates the HIF pathway and stimulates a coordinated erythropoietic response by increasing the production of endogenous erythropoietin to near physiologic levels and enhancing iron utilization.[2,3] In six pivotal Phase III trials (OLYMPUS, ANDES, ALPS, HIMALAYAS, SIERRAS, and ROCKIES) roxadustat has been demonstrated to effectively increase hemoglobin and iron availability in patients with anemia of NDD and DD CKD.[4]

AstraZeneca and FibroGen support patient-centric value assessments that comprehensively measure available data, costs and budget impacts, taking into consideration personalized approaches to care delivery while allowing ongoing access to innovative therapies that address unmet medical need. Based on the draft scoping document for roxadustat, AstraZeneca and FibroGen respectfully submit the following suggestions for your consideration.

Patient Population

As currently proposed, patient populations for consideration will include NDD, Incident Dialysis (ID), and DD CKD patients. Outcomes, co-morbidities, patient characteristics and treatment paradigms in these distinct patient populations are likely to differ and separation of patients with CKD according to these criteria at model baseline is appropriate. We encourage comparative value analysis of roxadustat in each of these three patient populations independently.

Clinically significant subgroups of patients have also been proposed in the draft scoping document including patients with inflammation (C-reactive protein > upper limit of normal), iron non-replete patients (TSAT < 20% or ferritin < 100 ng/mL), history of cardiovascular disease or cancer, and patients hyporesponsive to erythropoitin stimulating agent (ESA) treatment.[1] Subgroup analyses must be supported by clinical trial data, and care must be taken when extrapolating findings from the overall study cohort to patient subgroups.

Underlying differences in patient characteristics as well as healthcare reimbursement limitations may be some of the many factors that drive differences between countries in CKD anemia practice patterns, type of vascular access, use/availability of RBC transfusion and length of dialysis treatment.[5] The epidemiology of kidney disease can vary based on patient population. For example, compared to the rest of the world, patients in the US are more likely to have multiple comorbidities contributing to their CKD including diabetes mellitus and hypertension, and more likely to be inflamed, resulting in higher ESA doses.[6,7] Regarding the use of data from roxadustat studies conducted outside the US, we suggest these differences be taken into consideration.

Comparators and outcomes

Proposed comparators to roxadustat of darbepoetin alfa, epoetin alfa, methoxy polyethylene glycol-epoetin beta in NDD, DD and ID populations are appropriate, with the addition of usual care as represented by the placebo arm of the clinical trials in patients with NDD CKD. These comparisons should be performed with the understanding that the use of one of these ESAs is generally not random and outcomes may be confounded by the variables associated with the ESA choice.

Proposed outcomes of interest for comparative value analysis include hemoglobin control, requirement for blood transfusion, major adverse cardiovascular events (to include hospitalization for congestive heart failure episodes which are costly and confer their own mortality risk), and all-cause mortality which are appropriate for modelling differences in outcomes for DD and ID patients.[8] The proposed scope does not consider any modifications to the underlying course of CKD associated with different treatment strategies; we encourage the consideration of the impact of treatment on patient eGFR decline with roxadustat demonstrating a significant reduction in the rate of eGFR decline compared with placebo.[4,9] This finding has the potential to delay CKD progression in patients with NDD to more advanced stages of CKD or progression to ESRD. CKD progression is associated with increased resource utilization, poorer patient outcomes and reduced quality of life, and as such should be included as an outcome when assessing comparative effectiveness.[10]

In addition to active management of the anemia of CKD with ESA and potential requirement for blood transfusions, the use of IV iron should also be included as a relevant outcome; the use of ESAs often require concomitant IV iron supplementation, especially among those patients who are inflamed which can incur significant additional costs associated with administration. Differences in requirements for IV iron supplementation between NDD, ID, and DD CKD patients should also be considered, with guidelines suggesting a course of oral and/or IV iron before ESA therapy for many NDD patients.[1]

Costs

We would encourage ICER's analysis of comparative value to consider differences in specifically, relevant costs for NDD, ID, and DD patients. For example, in patients undergoing dialysis, treatment with roxadustat is not anticipated to reduce the requirements for renal replacement therapy, as such any direct costs associated with renal replacement therapy should be considered unrelated and therefore not included in the comparative effectiveness evaluation of roxadustat in DD or ID populations. This is of particular relevance given the high costs associated with the

provision of dialysis and the potential distorting effect upon any incremental cost utility ratio for any treatment with the potential to increase the lifespan in DD or ID patients.[11]

Comparative value analysis should include all relevant costs associated with non-ESA anemia therapy such as IV iron or blood transfusions, including costs associated with their administration in an outpatient clinic, urgent care, emergency department, or inpatient unit, any associated medical supplies, and any costs associated with adverse events related to their administration such as hypotension, infusion reaction, anaphylaxis or infection. In addition to these costs, evidence shows that receipt of blood transfusion can delay and reduce the chances of a successful subsequent blood transfusion as well as delay and reduce the probability of receiving a renal transplant as a result of allosensitization.[12]

Regarding bundled payments, the ESRD Prospective Payment System (PPS) is a unique population-based, payment system for patients on dialysis. Reimbursement is based on total anticipated costs across the patient population and averages payment across all treatments for all patients in the population; therefore, the payment rate is not based upon the quantity, quality, or value of individually furnished treatments provided to any given patient. We do not believe the statutorily imposed and capitated ESRD PPS payment rate results in cost data reflective of specific treatment value. In addition, approximately a quarter of Medicare patients with ESRD are currently covered under Medicare Advantage, which does not participate in the bundled payment rate. This is an important consideration given restrictions to ESRD patient enrollment in Medicare Advantage have been removed for 2021 and future years.

Direct costs associated with anemia treatment with ESA should consider reductions in responsiveness to treatment often related to an inflammatory process or inter-current event, requiring higher doses of ESA to maintain the same treatment effect. Higher ESA doses to maintain the desired Hb level are associated with increased acquisition costs and increased risk of major adverse cardiovascular events including stroke. These adverse events are particularly pronounced in the subgroup of patients who are hyporesponsive to ESA treatment. This subgroup of patients is estimated to represent up to 15% of patients with CKD receiving an ESA at any given time[13] with the majority of patients receiving treatment experiencing episodes of hyporesponsiveness in any given year.[14]

Modelling methodology

The proposed approach to modelling CKD based on the findings of the systematic literature review by Sugrue et al.[15] is appropriate. We would encourage the analysis to consider the impact of model cycle length on cost-effectiveness. Important considerations are that roxadustat has been demonstrated to rapidly correct patient's hemoglobin following treatment initiation and that NDD CKD patients enrolled in the roxadustat clinical trial program had advanced CKD with the propensity to rapidly progress to dialysis dependency. Model cycle length should be short enough to capture any differences between treatment strategies related to time to correction of anemia or time to renal replacement therapy.

Patient perspective

Patient preferences can impact a value assessment directly through patient satisfaction and indirectly through potential effects on adherence, demonstrated in the roxadustat clinical trial program where patients were more likely to remain on treatment with roxadustat than placebo.

We encourage consideration of patient preferences and potential effects on productivity in this review. Roxadustat is an oral therapy that can be conveniently administered at home or in an outpatient setting in contrast with currently available treatments for anemia of CKD. Employment-related outcomes including lost wages from absenteeism and presenteeism should be considered within scope for the value assessment, in addition to indirect costs associated with caregiver loss of productivity and work productivity loss for DD and NDD patient populations.

AstraZeneca and FibroGen appreciates your consideration of the enclosed comments. As you gather evidence and further plan the analyses, we hope that our comments assist in a fair assessment of roxadustat, based on scientific rigor and the highest quality evidence.

Respectfully,

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References

[1] Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney Int Suppl.* 2012;2:279-335. http://www.kdigo.org/clinical_practice_guidelines/pdf/KDIGO-Anemia%20GL.pdf. Accessed August 5, 2020.

[2] Dhillon S. Roxadustat: first global approval [published online ahead of print February 25, 2019]. Drugs. 2019. http://dx.doi.org/10.1007/s40265-019-01077-1. Accessed March 12, 2019.

[3] Del Vecchio L, Locatelli F. Roxadustat in the treatment of anaemia in chronic kidney disease. Expert Opin Investig Drugs. 2018;27:125-133.

[4] FibroGen. 2019. Press Release May 09 2019: FibroGen Announces Positive Topline Results from Pooled Safety Analyses of Roxadustat Global Phase 3 Program. https://fibrogen.gcs-web.com/news-releases/news-release-details/fibrogen-announces-positive-topline-results-pooled-safety. Accessed August 6, 2020.

[5] Robinson BM, Akizawa T, Jager KJ, et al. Factors affecting outcomes in patients reaching end-stage kidney disease worldwide: differences in access to renal replacement therapy, modality use, and haemodialysis practices. *Lancet*. 2016;388:294-306.

[6] Robinson BM, Zhang J, Morgenstern H, et al. Worldwide, mortality risk is high soon after initiation of hemodialysis. *Kidney Int*. 2014;85:158-165.

[7] Karaboyas A, Morgenstern H, Waechter S, et al. Low hemoglobin at hemodialysis initiation: an international study of anemia management and mortality in the early dialysis period. *Clin Kidney J*. 2019. http://dx.doi.org/10.1093/ckj/sfz065. Accessed June 23, 2020.

[8] Yarnoff BO, Hoerger TJ, Simpson SA, et al. The Cost-Effectiveness of Anemia Treatment for Persons with Chronic Kidney Disease. *PLoS One*. 2016;11:e0157323. Published 2016 Jul 12.

[9] FibroGen. 2020. Corporate Presentation June 2020. https://fibrogen.gcs-web.com/static-files/c456ad75-05bd-4b48-915c-84c3743dc3fb.

[10] Freeman C, Giles L, Field P et al. Humanistic burden and economic impact of chronic kidney disease: a systematic literature review [version 1; peer review: 1 approved, 2 not approved]. *F1000Research* 2019, 8:2142 (https://doi.org/10.12688/f1000research.21374.1).

[11] Grima DT, Bernard LM, Dunn ES, et al. Cost-effectiveness analysis of therapies for chronic kidney disease patients on dialysis: a case for excluding dialysis costs. *Pharmacoeconomics.* 2012;30(11):981-9.

[12] Fidler S, Swaminathan R, Lim W, et al. Peri-operative third party red blood cell transfusion in renal transplantation and the risk of antibody-mediated rejection and graft loss. *Transpl Immunol*. 2013;29(1-4):22-27.

[13] Rossert J, Gassmann-Mayer C, Frei D, McClellan W. Prevalence and predictors of epoetin hyporesponsiveness in chronic kidney disease patients. *Nephrol Dial Transplant.* 2007;22(3):794-800. doi:10.1093/ndt/gfl716.

[14] Luo J, Jensen DE, Maroni BJ, Brunelli SM. Spectrum and burden of erythropoiesis-stimulating agent hyporesponsiveness among contemporary hemodialysis patients. *Am J Kidney Dis.* 2016;68:763-771.

[15] Sugrue DM, Ward T, Rai S, McEwan P, van Haalen HGM. Economic Modelling of Chronic Kidney Disease: A Systematic Literature Review to Inform Conceptual Model Design. *Pharmacoeconomics.* 2019;37(12):1451-1468.