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Institute for Clinical and Economic Review
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To Whom It May Concern:

The American Society of Hematology (ASH) is pleased to offer comments on the Institute for Clinical and Economic Review's (ICER) Draft Scoping Document outlining its planned review of the comparative clinical effectiveness and value of emicizumab for prevention of bleeding in patients with hemophilia A who have inhibitors to coagulation factor VIII.

ASH represents over 17,000 clinicians and scientists worldwide, who are committed to the study and treatment of blood and blood-related diseases. These disorders encompass malignant hematologic disorders such as leukemia, lymphoma, and multiple myeloma, as well as non-malignant conditions such as sickle cell anemia, thalassemia, bone marrow failure, venous thromboembolism, and hemophilia. In addition, hematologists were pioneers in demonstrating the potential of treating various hematologic diseases; and we continue to be innovators in the field of stem cell biology, regenerative medicine, transfusion medicine, and gene therapy. ASH membership is comprised of basic, translational, and clinical scientists, as well as physicians who are providing care to patients in diverse settings including teaching and community hospitals, as well as private practices.

ASH is pleased with the Draft Scoping Document and offers the following comments:

Background

It should be noted that by far the most common and burdensome type of inhibitor is high-titer inhibitor, which requires "bypass" therapy. These inhibitors are associated with high costs, hospitalization, and morbidity. Those with low-titer inhibitors are by far the minority and require no bypass therapy and are not eligible for emicizumab.

On the top of page 2, it should be clarified that as many as 20 percent of those with new onset high-titer inhibitors do not respond to immune tolerance induction (ITI), and have greater morbidity than those who tolerate it. Furthermore, even in those who undergo ITI successfully, factor half-life is often shortened, requiring greater frequency of factor infusion (to match half-life) than a hemophilia patient without an inhibitor. It should be noted that those born prior to introduction of ITI, i.e. before 1980s, would not have been eligible to receive ITI, and if it is not introduced within

the first year of life, the patient cannot be tolerized. Further, the groups with high-titer inhibitors have a greater proportion from minority backgrounds and have greater health care disparity than non-inhibitor patients. Therefore, emicizumab would have a significant positive impact on this population.

Potential Major Advance for a Serious Ultra-Rare Condition

As ICER considers whether to use its value assessment framework for ultra-rare conditions, it should be noted that treatment with emicizumab for patients with hemophilia A with inhibitors not only offers potential major gains in quality of life but also a potential reduction in mortality given appreciable mortality associated with severe hemophilia and a high-titer inhibitor¹. Emicizumab clearly meets the third criterion for using this framework.

Identification of Low-Value Services

Individual hemophilia patients respond to treatments differently and ICER's analysis must recognize the heterogeneity of this patient population. When considering "wasteful or lower-value" services, it is critical that ICER avoid eliminating necessities for this condition that might be essential for a given patient.

Figure 2. Analytic Framework

In the model, it should be noted that the risks of thrombosis and thrombotic microangiopathy, were associated with the use of FEIBA (factor eight inhibitor bypass therapy). If the use of FEIBA is avoided (disallowed), then the downstream risks of the drug - thrombosis and microangiopathy - might be avoided and provide a more positive analysis. ASH suggests ICER perform the analysis with both scenarios, i.e. allowing the patient to take FEIBA as needed, or disallowing it altogether.

Analytic Framework

The Society encourages ICER to consider adding additional outcomes, including frequency of hospitalization; bleeding, needing red cell concentrates; and risk of thrombosis. The outcome of pain could include degree of opioid dependence.

Simulation Models Focusing on Long-term Value for Money

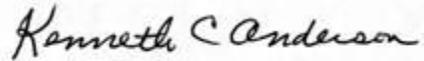
The model health states could also include hospitalization given attendant cost and cost of an adverse thrombotic event. Patients with an inhibitor have historically a high rate of hospitalization for acute bleeding, requiring inpatient infusion with treatment around the clock and often red cell transfusions. Consequently, this should be included in the model in terms of cost and morbidity. Furthermore, there is a potential danger signal with this new agent in terms

¹ Walsh, C. E., Soucie, J. M., Miller, C. H. and the United States Hemophilia Treatment Center Network (2015), Impact of inhibitors on hemophilia a mortality in the United States. Am. J. Hematol., 90: 400–405. doi:10.1002/ajh.23957

of thrombosis and thrombotic microangiopathy so the models should also include the morbidity and mortality of a thrombotic event.

Thank you for the opportunity to provide these comments. We welcome the opportunity to discuss these proposals and others being considered with you and your team. If you have questions or require further clarification, please contact Leslie Brady, ASH Policy and Practice Manager, at lbrady@hematology.org or 202-292-0264.

Sincerely,

A handwritten signature in black ink that reads "Kenneth C. Anderson". The signature is written in a cursive style with a clear, legible font.

Kenneth C. Anderson
President

September 29, 2017

Institute for Clinical and Economic Review (ICER)
2 Liberty Square
Boston, MA 02109

RE: Response to ICER's Draft Scoping Document to assess the value of emicizumab for hemophilia A patients with inhibitors.

Dear ICER Review Panel:

Genentech, a Member of the Roche Group, appreciates the opportunity to provide comments as ICER begins developing the scoping document for review of emicizumab for hemophilia A patients with inhibitors. On behalf of Genentech, and in the interest of patients with hemophilia A with inhibitors who need the choice of and access to impactful and / or life-saving treatments, we propose the following:

We suggest that ICER evaluate emicizumab under the proposed framework for ultra-rare conditions to account for the nuances of evaluating rare disease therapies, including small sample sizes and heterogeneity of data. We feel that emicizumab would qualify for review under the current proposed criteria:

- *“Indicated to treat a condition that affects <10,000 patients”*
 - Emicizumab is currently under review by the FDA for use in patients with hemophilia A with FVIII inhibitors. This patient population is estimated to be less than 1,200 in the United States, inclusive of patients on immune tolerance induction.¹
- *“Little chance of expanding the indication such that the patient population eligible to receive the treatment exceeds 20,000 patients”*
 - Emicizumab is currently being studied for treatment of patients with hemophilia A, who have missing or impaired functioning of FVIII. In the United States, the total US hemophilia A patient population is estimated to be less than 20,000 (World Federation of Hemophilia - WFH N=14,175, CDC 10.5 cases/100,000 males).²⁻⁴
- *“The treatment has the potential to offer a major gain in improved quality of life”*
 - Emicizumab has the potential to offer a major gain in improved quality of life for patients with hemophilia A with inhibitors.
 - Statistically significant and clinically meaningful differences were seen in health-related quality of life and health status scores for patients who received emicizumab compared with patients who only received episodic bypassing agents (BPA) during the randomized portion of HAVEN 1.⁵

We commend ICER for recommending the identification of lower-value services used in the management of hemophilia that could be reduced or eliminated from health care budgets and replaced by high-value innovative services. Please consider the following services that may be impacted should emicizumab become available as a treatment option:

- Reduction in the use of central venous access devices (CVAD)
 - Emicizumab is administered by subcutaneous injection, and does not require the insertion a CVAD. The elimination of a CVAD will reduce the associated healthcare resource utilization and costs of CVAD insertion and maintenance, as well as costs associated with complications of such devices such as infection and thrombosis.⁶
- Reduction in treated bleeds
 - In HAVEN 1, emicizumab (Arm A) demonstrated an 87% reduction in the annualized treated bleed rate (ABR) compared to episodic BPA (Arm B) (2.9 vs 23.3 events/year).⁵ Inpatient comparison in patients previously on BPA prophylaxis (Arm C) showed a 79% reduction in ABR after switching to emicizumab (15.7 vs 3.3 events/year).⁵ In an interim analysis of HAVEN 2, 18/19 (94.7%) patients had experienced zero treated bleeds while receiving emicizumab prophylaxis.⁷ The reduction in the rate of treated bleeds over time may reduce the need for imaging studies to assess bleeds, as well as the treatment and management of bleeds, potential complications, joint replacements and associated costs.
- Reduction of joint damage
 - Recurrent bleeding into target joints results in progressive joint damage and potentially hemophilic arthropathy.⁸ Prophylactic infusions with currently available products have been shown to lead to better joint-related outcomes.⁹
 - The use of services and devices that may be reduced with an overall decrease in the occurrence of joint damage with increased use of prophylaxis include, but are not limited to, physical therapy, physician visits, and durable medical equipment.
- Immune tolerance induction (ITI)
 - In HAVEN 1, 14/35 (40%) patients in Arm A and 7/18 (39%) patients in Arm B had previous ITI.⁵ Currently, the WFH recommends ITI for patients with inhibitors.¹⁰ Although there is no standard regimen, ITI generally involves administering large doses of FVIII concentrates on a regular basis for a period of months to years.^{10,11} There is significant cost associated with ITI therapy, as well as burden to patients and families.¹² Once emicizumab is approved, it potentially could impact physician and patient choice to forgo ITI therapy due to the duration, cost and/or treatment burden, or reduce the duration of time a patient is willing to undergo ITI therapy for the same reasons.

We agree with ICER's decision to include all age groups in the review; however:

- Consider adhering to the two age groups studied in the HAVEN 1 and HAVEN 2 clinical trials: adults/adolescents ≥ 12 years old and children < 12 (inclusive of children < 2).^{5,7}

We agree with ICER's acknowledgement of the significant impact hemophilia A has on patients, caregivers and society. We urge ICER to consider how to incorporate these attributes into their value assessment:

- Failure to include important attributes into the value assessment because they cannot be captured by the quality-adjusted-life year (QALY) may underestimate the full impact of emicizumab on patients, their families and caregivers. Such attributes include, but are not limited to:
 - Impact of increased bleeding-related morbidity and mortality in patients with hemophilia A with inhibitors.¹⁵
 - Time off of school and work due to breakthrough bleeding events.¹⁶
 - Pain and functional impairment affecting employment, relationships, daily activities and perceived quality of life.^{17,18}
 - Frequent infusion time and/or extended infusions, can result in poor compliance and inferior treatment outcomes, such as higher incidence of breakthrough bleeds leading to joint damage and disability.¹⁹⁻²¹
- In addition, we strongly recommend ICER consider the methodological concerns associated with use of the QALY in rare diseases such as hemophilia. QALYs are heavily weighted instruments used to derive preferences and are developed on population averages. Use of QALYs in rare diseases, for which limited data are available, may preclude the ability to accurately characterize the value that patients and their families derive from treatment.²²

ICER noted that, where data permitting, they will consider combined use of direct and indirect evidence in network meta-analysis of selected outcomes. Please consider the following limitations with conducting such an analysis:

- Limited data availability and variable length of follow-up.
- Heterogeneity of the data (e.g., inclusion of patients with hemophilia A and B).
- Inconsistent reporting of outcomes and adverse events.

In closing, we thank you for the opportunity to comment on the draft scoping document for emicizumab and we hope that these comments will contribute to a more meaningful assessment. We welcome the opportunity to provide clarification should ICER have any questions. Please contact me directly at (650) 243 7134 or hansen.jan@gene.com.

Respectfully Submitted,



Jan Hansen PhD
Vice President, Evidence for Access
Genentech US Medical Affairs

References:

1. Wight J and Paisley S. The epidemiology of inhibitors in haemophilia A: a systematic review. *Haemophilia* 2003;9(4):418-435.
2. World Federation of Hemophilia (WFH). Annual Global Survey 2015. Available at: <http://www1.wfh.org/publication/files/pdf-1669.pdf>. Accessed 09/20/17
3. Centers for Disease Control and Prevention. Hemophilia. Data and Statistics. <http://www.cdc.gov/ncbddd/hemophilia/data.html>. Accessed 09/22/2017
4. Soucie JM, Evatt B, Jackson D. Occurrence of hemophilia in the United States. The Hemophilia Surveillance System Project Investigators. *Am J Hematol*. Dec 1998;59(4):288-294. <http://www.ncbi.nlm.nih.gov/pubmed/9840909>
5. Oldenburg J, Mahlangu JN, Kim B, et al. Efficacy of emicizumab prophylaxis in hemophilia A with inhibitors [supplementary appendix appears online]. *N Engl J Med* 2017; 377:809-818. <http://www.ncbi.nlm.nih.gov/pubmed/28691557>
6. Valentino LA, Ewenstein B, Navickis RJ, et al. Central venous access devices in haemophilia. *Haemophilia*. Mar 2004;10(2):134-146. <http://www.ncbi.nlm.nih.gov/pubmed/14962202>
7. Young G, Oldenburg J, Liesner R et al. HAVEN 2: Efficacy, safety and pharmacokinetic of once-weekly prophylactic emicizumab (ACE910) in pediatric patients (<12 years) with hemophilia A with inhibitors: interim analysis of single-arm, multicenter, open-label, phase 3 study. Presented at the 26th Biennial Congress of the International Society on Thrombosis and Haemostasis and 63rd Annual Scientific and Standardization Committee (SSC) Meeting in Berlin, Germany; July 8-13,2017. ISTH Abstract #OC24.1.
8. Valentino LA. Blood-induced joint disease: the pathophysiology of hemophilic arthropathy. *J Thromb Haemost* 2010; 8(9):1895-1902. <http://www.ncbi.nlm.nih.gov/pubmed/20586922>
9. Manco-Johnson MJ, Abshire TC, Shapiro AD, et al. Prophylaxis versus Episodic Treatment to Prevent Joint Disease in Boys with Severe Hemophilia *N Engl J Med* 2007; 357: 535-544.
10. Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al. Guidelines for the management of hemophilia. *Haemophilia*. Jan 2013;19(1):e1-47. <http://www.ncbi.nlm.nih.gov/pubmed/22776238>
11. Valentino LA, Kempton CL, Kruse-Jarres R, et al. US Guidelines for immune tolerance induction in patients with haemophilia a and inhibitors. *Haemophilia*. Sep 2015;21(5):559-567. <http://www.ncbi.nlm.nih.gov/pubmed/26032231>
12. Su et al. The Immune Tolerance Induction Factor Utilizations and Costs for the Management of Male Hemophilia-a Patients Who Developed Inhibitors. *Blood* 2016; 128: 4758-

13. Leissinger C, Gringeri A, Antmen B, et al. Anti-inhibitor coagulant complex prophylaxis in hemophilia with inhibitors. *N Engl J Med*. Nov 03 2011;365(18):1684-1692. <http://www.ncbi.nlm.nih.gov/pubmed/22047559>
14. Ryu JE, Park YS, Yoo KY, Lee KD, Choi YM. Immune tolerance induction in patients with severe hemophilia A with inhibitors. *Blood Res*. Dec 2015;50(4):248-253. <http://www.ncbi.nlm.nih.gov/pubmed/26770953>
15. Walsh CE, Soucie JM, Miller CH, United States Hemophilia Treatment Center N. Impact of inhibitors on hemophilia A mortality in the United States. *Am J Hematol*. May 2015;90(5):400-405. <http://www.ncbi.nlm.nih.gov/pubmed/25616111>
16. Recht M, Neufeld EJ, Sharma VR, et al. Impact of acute bleeding on daily activities of patients with congenital hemophilia with inhibitors and their caregivers and families: observations from the Dosing Observational Study in Hemophilia (DOSE). *Value Health*. Sep 2014;17(6):744-748. <http://www.ncbi.nlm.nih.gov/pubmed/25236999>
17. Curtis R, Baker J, Riske B, et al. Young adults with hemophilia in the U.S.: demographics, comorbidities, and health status. *Am J Hematol*. Dec 2015;90 Suppl 2:S11-16. <http://www.ncbi.nlm.nih.gov/pubmed/26619192>
18. Witkop M, Guelcher C, Forsyth A, et al. Treatment outcomes, quality of life, and impact of hemophilia on young adults (aged 18-30 years) with hemophilia. *Am J Hematol*. Dec 2015;90 Suppl 2:S3-10. <http://www.ncbi.nlm.nih.gov/pubmed/26619194>
19. Khair K. Minimizing joint damage: the role of nurses in promoting adherence to hemophilia treatment. *Orthop Nurs* 2010;29:193–200.
20. Martin LR, Williams SL, Haskard KB, Dimatteo MR. The challenge of patient adherence. *Ther Clin Risk Manag* 2005;1:189–99.
21. Klamroth R, Pollmann H, Hermans C, et al. The relative burden of hemophilia A and the impact of target joint development on health-related quality of life: results from the ADVATE Post-Authorization Safety Surveillance (PASS) study. *Hemophilia* 2011;17:412–21.
22. Measuring Value in Medicine: Uses and Misuses of the QALY. Partnership to Improve Patient Care. June 2017. Available at: <http://www.pipcpatients.org/resources/white-paper-uses-and-misuses-of-the-qaly-ethical-issues-and-alternative-measures-of-value>

September 29, 2017

Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Re: Emicizumab for Hemophilia A Effectiveness and Value: Draft Background and Scope

To Whom It May Concern:

The National Hemophilia Foundation (NHF) and the Hemophilia Federation of America (HFA) are national non-profit organizations that represent individuals with bleeding disorders across the United States. Our missions are to ensure that individuals affected by hemophilia and other inherited bleeding disorders have timely access to quality medical care, therapies, and services, regardless of financial circumstances or place of residence. Both organizations accomplish this through advocacy, education, and research. Hemophilia A and B are rare, chronic bleeding disorders affecting approximately 20,000 individuals in the US. In addition to hemophilia A and B, there are a number of even more rare factor deficiencies, such as factor I, II, V, VII, X, XI, XII and XIII deficiencies. Both NHF and HFA serve patients with these deficiencies as well.

We appreciate the opportunity to provide comment to the Institute for Clinical and Economic Review (ICER) draft background and scope for review of Emicizumab. Our comments follow by section of the document:

Potential Major Advance for a Serious Ultra-Rare Condition: Ultra-Rare Disease Framework

While we appreciate that the ICER Value Framework for the Assessment of Treatment for Ultra-Rare Conditions is not yet finalized, based on our review of the document, we believe it is the appropriate framework for evaluation of Emicizumab. We encourage ICER to reconsider its preliminary plan to evaluate Emicizumab under the usual ICER value framework. The precedent set by this determination is important not only for this review but future advancements in the care of hemophilia. Emicizumab clearly fits within the three criteria proposed for use of the ultra-rare disease framework:

- The treatment is envisaged for a patient population of fewer than 10,000 individuals - At this time, Emicizumab is only seeking an indication for treatment of persons with hemophilia (PWH) with inhibitors. According to the latest dataset (June 30, 2017) reported in the American Thrombosis and Hemostasis Network (ATHN) Research Report – which describes the national surveillance program for the bleeding disorders community – there are 1,564 PWH FVIII with inhibitors registered within the U.S. Hemophilia Treatment Center network. This is well below the threshold of 10,000.
- There is little chance of future expansion of indication or population that would extend the size of the treated population above 20,000 individuals - If at some point Emicizumab were to file for and receive an expanded indication for treatment of PWH without inhibitors, the number of eligible PWH would expand, but even then, the size of the potential population would be below the threshold of 20,000. On-going studies for this expanded indication are enrolling PWH FVIII with severe level of factor deficiency. In any calculation of potential population size, PWH FIX should be excluded from the long-term estimate of potential patients since the mechanism of action for Emicizumab means that it would not be used for the FIX subtype. Based on current prevalence estimates, Hemophilia A (type: FVIII) represents only 80-85% of the total US PWH population. ATHN data indicate there are 11,219 PWH FVIII receiving care within the federally-funded hemophilia treatment centers (HTCs) network. For those PWH FVIII with a known genotypic classification ATHN

reports the count by disease severity classification to be: Severe 50.6% (5,682 PWH), Moderate 16.3% (1,830 PWH), and Mild 29.8% (3,344 PWH). Additional research has estimated that there are an additional ~2,500 PWH FVIII who receive care outside the HTC system¹. This represents patients of all severity classifications. While the HAVEN studies for non-inhibitor PWH enrolled only those with a severe genotype, if an indication for non-inhibitor PWH prophylaxis is obtained then some number of moderate and mild patients would treat with Emicizumab. However, it would be inappropriate to assume that 100% of PWH FVIII across all severities would aspire to prophylaxis with Emicizumab. PWH are genotypically and phenotypically unique, and bleeding frequency, severity and patient preferences differ. Today, we would not anticipate all PWH FVIII, particularly those with milder phenotypes, would be within the target population. Based on these data, it is clear there is little chance of a future expansion that would extend the size of the population above 20,000 individuals.

- The treatment potentially offers a major gain in improved quality of life and/or length of life - Emicizumab has the potential to offer a major gain in improved quality of life and/or length of life for those PWH VIII living with an inhibitor. The published HAVEN data, coupled with the anecdotal reports received by NHF and HFA, clearly demonstrate the potential for Emicizumab to deliver a life-changing treatment paradigm.

Low Value Services

While not technically “wasteful or lower-value services used in the management of PWH” as these are essential to the current paradigm of treatment, there are several aspects of the current care delivery model and treatment where offsetting system savings might be achieved:

- Transition to a subcutaneous therapy from an IV therapy would reduce or likely substantially mitigate a number of current treatment costs and burdens e.g., the need for home health care services, in-home nursing support, placement of ports (and their management including infections), and challenges of venous access in aging populations.
- Episodes of acute and long-term chronic pain are well known aspects of living with hemophilia. Previously-unavailable prophylactic preventive treatment likely will reduce the need for pain management and concomitant medications used for pain relief. The cost and challenges of opioid management are in increasingly significant cost and burden on health systems.
- Reduction in the need for or duration of Immune Tolerance Induction (ITI).
- Reduction in bleeding episodes and long term joint damage resulting in savings in factor replacement therapy, physical therapy/rehabilitation, and corrective orthopedic surgery.

Populations

The methodology section indicates that ICER does not plan to model children younger than 2 years old as it does not expect to have adequate evidence for this group. It is well recognized that early initiation of prophylaxis (immediately after the first joint or significant muscle bleeding episode) is important to prevent long-term joint disease. We are concerned the absence of evidence in the youngest age band could be misinterpreted. Without other rationale (e.g., treatment safety concerns), age should not be an arbitrary cutoff for determination of when it is most effective to begin prophylaxis. Instead of three age bands, we would recommend that ICER model those < age 12 and ≥ age 12. This would also correspond with the age ranges within the HAVEN studies and available data.

Interventions

No comments

Comparators

An additional comparison could be to explore prophylaxis with Emicizumab for PWH with inhibitors vs. immune tolerance Induction (ITI). A substantial number of patients may not have complete responses to ITI owing to the presence of persistent low-level inhibitors. ITI partial or complete success is reported in ~70% of PWH. Achieving success to ITI takes 12 months on average, but some patients may remain on ITI for years and require on-going exposure to FVIII (prophylaxis).² Additionally, ITI may be used concomitantly with other drugs which have the potential for side effects (e.g., rituximab). The burden of treatment for PWH with inhibitors and their caregivers while on an intensive ITI regime is immense. ITI is associated with higher costs, at least initially, when compared to prophylactic treatment with by-pass agents.³

If an additional comparative analysis for ITI is not included within the evaluation, please consider a prominent comment within the report executive summary which indicates there are other potential and significant health system cost savings which might be achieved if the introduction of Emicizumab leads to a change in clinical practice for ITI.

Outcomes

We are pleased that ICER is proposing to use a broad group of outcomes that are important to patients. We offer the following comments to bolster this analysis:

- We are pleased ICER has proposed to analyze pain as an independent outcome. We do not believe generic, composite health-related quality of life scores have sufficient sensitivity to distinguish change in this important domain. PWH, especially those with inhibitors, frequently experience both episodes of acute and persistent chronic pain. Generic instruments that simply incorporate health status “today” do not sufficiently capture the magnitude of pain’s interference on daily activity and functioning.
- In addition to pain, we would urge ICER to consider subdomain analysis of mobility (activity), and anxiety and depression. Based on reports from study participants we believe these too will be important variables in the value equation.
- Beyond those outcomes specifically reported within the clinical trials, there are other significant benefits which will contribute to the long-term value of paradigm-shifting treatments such as Emicizumab. These “other benefits and disadvantages” should remain a primary consideration in ICER’s value calculations. We urge ICER to acknowledge the importance of the associated productivity and offsets for patients and their caregivers. Given PWH with inhibitors are an ultra-rare subpopulation with the rare disease of hemophilia, there will naturally be a paucity of high-level data. We are concerned there will be a tendency to diminish the importance of these additional “contextual considerations.” In looking at the long-term value of elements such as career, educational, and employment choices appropriate discount rates should be considered that take into account the long-term value of the health effects in relation to the costs. These are elements which will yield benefit over a lifetime, well beyond the duration of a limited observational study.
- The absence of available utility data should not lead ICER automatically to exclude other patient-relevant outcomes from the evaluation. As many of the listed patient-relevant outcomes are not

typically captured in public health surveillance systems nor were they fully anticipated and collected within the pivotal clinical studies for Emicizumab, ICER will need to consider low level or indirect evidence when head-to-head studies or comparative data are not available. If not suitable for formal inclusion within the economic model, we encourage ICER to prominently discuss the added patient-relevant outcomes in any executive summary rather than leave them to recommendations for future research.

Timing

We encourage ICER to take a long-term whole-of-life view when considering the potential benefits and harms of prophylactic treatment with Emicizumab. Any economic evaluation should include appropriate allowance for consideration of those outcomes that are both substantial in effect and sustained over an extended period of time.

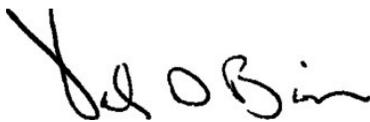
Settings

No comments

Conclusion

We appreciate the opportunity to provide these comments. Please contact Michelle Rice, NHF's Senior Vice President for External Affairs and Katie Verb, HFA's Director of Policy & Government Relations with any questions.

Sincerely,



Val Bias
Chief Executive Officer
National Hemophilia Foundation



Kimberly Haugstad
President & CEO
Hemophilia Federation of America

¹ Owens WE, Oakley MA, Le, BC, Byams VR. Public Health Surveillance of People Not Receiving Care at US Federally-funded Hemophilia Treatment Centers: Treatment, Sources, and Utilization of Healthcare in the CHOICE Project. Poster presented at: 58th ASH Annual Meeting & Exposition; 2016 Dec 3-6; San Diego, CA.

² Valentino, L. A., Kempton, C. L., Kruse-Jarres, R., Mathew, P., Meeks, S. L., Reiss, U. M. and the International Immune Tolerance Induction Study Investigators (2015), US Guidelines for immune tolerance induction in patients with haemophilia a and inhibitors. *Haemophilia*, 21: 559–567. doi:10.1111/hae.12730

³ Earnshaw, S. R., Graham, C. N., McDade, C. L., Spears, J. B. and Kessler, C. M. (2015), Factor VIII alloantibody inhibitors: cost analysis of immune tolerance induction vs. prophylaxis and on-demand with bypass treatment. *Haemophilia*, 21: 310–319. doi:10.1111/hae.12621



September 29, 2017

Steven D. Pearson, MD, MSc, FRCP
President, Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, MA 02109 USA
Submitted electronically via: publiccomments@icer-review.org

Re: Shire's Response to the Draft Scoping Document for the Institute for Clinical and Economic Review (ICER) Evaluation of Emicizumab for Hemophilia A with Inhibitors

Dear Dr. Pearson:

Shire appreciates the opportunity to submit comments on the proposed scope for ICER's value assessment of emicizumab for patients with hemophilia A with inhibitors. Shire is the global leader in rare diseases and is a long-standing partner in the hemophilia community, working to improve patient outcomes and access to our existing treatments for hemophilia by reducing barriers to access, driving innovation to individualize treatment, and prioritizing the safety of our therapies. To that end, Shire has reported over 40 years of real-world safety experience with an estimated 2 million infusions with FEIBA in the hemophilia inhibitor population¹.

Hemophilia A with inhibitors is an ultra-rare condition in which treatment decisions require complex and personalized clinical, safety, and ethical considerations. The total population of hemophilia A and B in the US is estimated to be 20,000 by the CDC², of which hemophilia A represents approximately 79%³ or 15,800. The WFH global annual report in 2013 estimated that the prevalence of hemophilia A patients with active inhibitors is 895 in the United States⁴. Shire is aligned with many of the points made in ICER's white paper on Assessing the Effectiveness and Value of Drugs for Rare Conditions⁵, which highlighted key challenges in the framework, evidence and methodology for assessing the value of ultra-rare conditions.

Shire offers a summary of our recommendations on the draft scoping document.

I. We encourage ICER to reconsider making a conclusive evaluation of emicizumab given the limited evidence to conduct a meaningful comparative effectiveness analysis and economic modeling in the ultra-rare population of hemophilia A with inhibitors.

The limited number of clinical and real-world studies have substantial differences in study design, patient population, comparators, and endpoints, making it extremely challenging to assess comparative effectiveness and cost-effectiveness.

II. The proposed analytical framework for the value assessment of emicizumab contains the following methodological challenges that ICER should consider for clarification:

- a. Endpoints are not consistently reported across studies in hemophilia with inhibitors. ICER has listed “treated bleeds”, “treated joint bleeds”, and “treated target joint bleeds” as outcome measures. These endpoints have not been designed in previous protocols or reported in prophylaxis studies of FEIBA or NovoSeven. Instead, prior publications on prophylaxis in the hemophilia inhibitor population consistently reported on all bleeds, all joint bleeds, and/or all target joint bleeds⁶⁻⁸. It is not clear how cross-trial comparisons can be made unless there is clarity in endpoints and consistency across trials.
- b. The definition of a target joint has evolved since the 2014 ISTH recommendation⁹, suggesting that a target joint be defined as “three or more spontaneous bleeds into a single joint within a consecutive 6-month period.” Prior to the 2014 ISTH recommendation, some studies have used ≥ 4 bleeds in 6 months⁶, making comparisons between studies challenging.
- c. The model health states proposed by ICER are not mutually exclusive. As an example, a patient could be treated for a target joint bleed and have arthropathy at the same time. In a health state transition model, an individual must be in only one state during each model cycle.

Hemophilia A with inhibitors is a complex disease where the tailoring of different treatment options for individual patients across treatment settings should be directed by hemophilia treaters. One randomized controlled study¹⁰ in inhibitor patients demonstrated that patients have discordant responses to different bypass therapies, highlighting the heterogeneity of the population and the need to ensure access to all approved treatments for hemophilia patients with inhibitors. Decreasing access to any one of the currently marketed bypass therapies may put patients at risk of: (a) having no effective treatment for breakthrough bleeds or hemostatic coverage during surgery; or (b) experiencing avoidable adverse events if bypassing agents are needed for breakthrough bleed treatment while on emicizumab.

Shire is committed to continuing to understand and respond to the unmet needs of inhibitor patients, their families and caregivers. We appreciate ICER for considering our concerns and

I look forward to continuing to collaborate with ICER on the emicizumab value assessment. Please feel free to contact us should you wish to discuss in further detail.

Sincerely,

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References

1. Crea R, Novack A, Reininger AJ et al. *Blood*. 2017;128:5031
2. <https://www.cdc.gov/ncbddd/hemophilia/data.html> Accessed September 15, 2017
3. Soucie et al, *American Journal of Hematology*, 1998, 59:288–294
4. <http://www1.wfh.org/publications/files/pdf-1591.pdf> Accessed September 15, 2017
5. *Assessing the Effectiveness and Value of Drugs for Rare Conditions*. May 2017. Available at https://icer-review.org/wp-content/uploads/2017/02/ICER_Assessing-the-Value-of-Drugs-for-Rare-Conditions_051017.pdf. Accessed September 3, 2017
6. Antunes et al. *Haemophilia*. 2014 Jan;20(1):65-72
7. Leissenger C et al. *N Engl J Med*. 2011;365(18):1684-1692
8. Konkle BA, Ebbesen LS, Erhardtsen E, et al. *J Thromb Haemost*. 2007;5(9):1904-1913.
9. Blanchette V et al. *J Thromb Haemost*. 2014;12(11):1935-1939
10. Astermark J et al. *Blood*, 2007; 109 (2): 546-551