

American Thrombosis and Hemostasis Network

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February 12, 2020

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

RE: Valoctocogene Roxaparvovec and Emicizumab for Hemophilia A: Effectiveness and Value

To Whom it May Concern:

In my role as Chief Science Officer of the American Thrombosis and Hemostasis Network (ATHN), I would like to take this opportunity to comment on ICER's proposed analysis of the effectiveness and value of BioMarin's Valoctocogene Roxaparvovec (valrox). In particular, I would like to help ICER understand the potential impact in terms of the number of patients who could potentially benefit from therapy with valrox. The goal of this comment will be to demonstrate the limited number of potential recipients of valrox. The potential population impact of valrox is important as the value of the medication should be viewed through the lens of a therapy for people with an ultra-rare medical condition.

The population of potential recipients of valrox includes:

- Severe hemophilia A
- Age \geq 18 years
- No current or history of factor VIII inhibitor
- No active infections/immunosuppression
- No active liver disease or cirrhosis
- No pre-existing antibodies to AAV5

After FDA approval, a source of payment will also be mandatory. So, in the US, having insurance covering the cost of this medication and monitoring after administration will be mandatory.

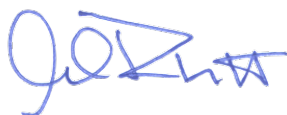
Based on these criteria, I would estimate approximately 2000 patients in the US could potentially be recipients of valrox:

Criteria	# of potential recipients
People in United States with hemophilia ¹	17,000
Percentage with hemophilia A (80%) ²	13,600
Percentage with severe hemophilia A (60%) ²	8,200
Percent without AAV5 inhibitory antibody (75%) ³	6,100
Percent with some sort of health insurance (90%) ⁴	5,500
Percent without a high deductible health plan (75%) ⁵	4,100
Percent \geq 18 years of age (75%) ⁶	3,100
Percent without a current inhibitor or history of inhibitor to FVIII (70%) ⁷	2,200
Percent without other exclusionary comorbidities (80%) ⁸	1,700

Based on these population statistics, the value of valrox should be appraised in the setting of an ultra-rare medical condition as the potential number of recipients of this medication in the United States is fewer than 2000 individuals.

I appreciate the opportunity to comment on ICER's document "Valoctocogene Roxaparvovec and Emicizumab for Hemophilia A: Effectiveness and Value."

Sincerely,



Michael Recht, MD, PhD, MBA
 Chief Science Officer
 American Thrombosis and Hemostasis Network

Professor of Pediatrics and Medicine
 Oregon Health & Science University

Disclosures: My academic institution (Oregon Health & Science University) has received research funding for participating in clinical trials sponsored by BioMarin and Roche/Genentech. In addition, I have received fees (< \$5000) as a consultant for Roche/Genentech. In addition, ATHN has received funding for projects from both BioMarin and Roche/Genentech.

¹ Soucie et al, Am J Hematol, 1998 Dec; 59(4):288-94

² <https://www.cdc.gov/ncbddd/hemophilia/data.html>. Accessed 08 Feb 2020

³ Stanford et al, Res Pract Thromb Haemost, 2019 Apr; 3(2):261-267

⁴ <https://www.census.gov/library/publications/2018/demo/p60-264.html>. Accessed 10 Feb 2020

⁵ Kullgren et al, Health Affairs, 2019 Mar; 38(3)

⁶ <https://www.census.gov/prod/cen2010/briefs/c2010br-03.pdf>. Accessed 10 Feb 2020

⁷ Witmer and Young, Ther Adv Hematol, 2013 Feb, 4(1):59-72

⁸ Personal experience enrolling potential participants on hemophilia A gene therapy clinical trials

February 13, 2020

Steven D. Pearson, MD, MSc
President
Institute for Clinical & Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Re: Comments on “Valoctocogene Roxaparvovec and Emicizumab for Hemophilia A: Effectiveness and Value – Draft Background & Scope”

Dear Dr. Pearson:

On behalf of BioMarin, I appreciate the opportunity to provide comment on the Institute for Clinical & Economic Review (ICER)’s draft scoping document for the ongoing assessment of valoctocogene roxaparvovec, BioMarin’s investigational gene therapy for hemophilia A.

BioMarin appreciates ICER’s efforts to appropriately consider the full set of benefits that ultra-rare disease therapies – including valoctocogene roxaparvovec – can provide to patients, their families, the healthcare system, and society. The purpose of this letter is to provide input on ICER’s Draft Background and Scope for the assessment of valoctocogene roxaparvovec, posted on January 24, 2020. Our comments focus on the aspects of Population, Framework, Comparators, Outcomes.

Population: Valoctocogene roxaparvovec was clinically investigated in a population of adults with severe hemophilia A. Therefore, evaluation in a population of adults with severe hemophilia A will support the most relevant assessment.

The draft scoping document states: “The population of focus for this review will be people with hemophilia A without inhibitors to factor VIII. For valoctocogene roxaparvovec, there should be consideration made for limiting the review to an adult population.” For greatest relevance and applicability of this assessment, we advocate for aligning the population in the review with the population studied in the valoctocogene roxaparvovec clinical program and with the expected eligible patient population. We therefore recommend that the assessment population should be limited to adults with severe hemophilia A, without inhibitors, who are currently managed with the most clinically appropriate standard of care for their disease severity (typically recombinant factor VIII (FVIII) prophylaxis). Key inclusion/exclusion criteria from the valoctocogene roxaparvovec clinical programs are as follows:^{1,2}

- Males \geq 18 years of age^{3,4,i}
- Diagnosis of severe hemophilia A^{5,ii}
- No previously documented history of a detectable FVIII inhibitor⁶
- No significant liver dysfunction or significant liver fibrosis
- No evidence of an active infection or any immunosuppressive disorder^{7,iii}
- Prior prophylaxis therapy^{8,iv}
- No detectable pre-existing antibodies to the AAV5 capsid⁹

ⁱ US Census data were used to calculate the proportion of individuals in the from the age categories presented in the WFH survey.

ⁱⁱBMN 270 eligible patients are those with severe disease, age \geq 18. Severity stratification data for this figure was calculated from a male population \geq 20 years (Source: CDC 2019).

ⁱⁱⁱ HIV/HSV/HCV prevalence is expected to vary by age cohort. HIV/HSV/HCV negative status estimates for populations 18-25 years and $>$ 25 years of age are 100% (assumption) and 65%,⁷ respectively.

^{iv} This value is sourced from a hemophilia A population treated at HTC and could be a slight over-estimation of prior prophylaxis use in a general adult hemophilia A population.

Dr. Steven Pearson

Re: Comments on “Valoctocogene Roxaparvovec and Emicizumab for Hemophilia A: Effectiveness and Value – Draft Background & Scope”

Based on the criteria listed above, BioMarin estimates that the US prevalence in individuals who would be eligible for valoctocogene roxaparvovec once approved would be 1,704. While BioMarin's perspective is that the above criteria demonstrate appropriate utilization for valoctocogene roxaparvovec, even in a scenario where the population were limited to adults with severe hemophilia A, the estimated prevalence would fall well below ICER's ultra-rare threshold at 5,082 persons with hemophilia A.

Framework: Given the small size of the intended patient population and the attributes of valoctocogene roxaparvovec, evaluation using both the Ultra-Rare and the Single or Short-Term Therapies (SST) frameworks is most appropriate.

In accordance with the updated ICER value framework finalized January 2020, ICER has designed modified criteria for ultra-rare disease therapies and SSTs to be applied where appropriate with the goal of supporting balance between incentives for innovation, access, and affordability. BioMarin considers valoctocogene roxaparvovec to be eligible for both the ultra-rare disease¹⁰ and SST¹¹ value framework modifications.

Per the above, BioMarin estimates 1,704 US individuals are eligible for valoctocogene roxaparvovec, thus remaining well below the ultra-rare population definition of 10,000. Further, valoctocogene roxaparvovec is administered via a one-time single intravenous infusion and has been demonstrated to have a significant effect on clinical and patient-relevant outcomes, including FVIII activity levels, annualized bleeding rate, annualized FVIII utilization, and health related quality of life.

Published data from the Phase 1/2 clinical study of valoctocogene roxaparvovec¹² demonstrated that three years after receiving a single 6×10^{13} vg/kg dose of valoctocogene roxaparvovec, participants expressed FVIII levels within the ranges defined as moderate (one participant), mild (five participants), and non-hemophilic (one participant), as determined by the more conservative chromogenic substrate (CS) assay. By one-stage (OS) assay, all participants demonstrated FVIII levels within the mild (six participants) and non-hemophilic (one participant) ranges at the end of year three. At this timepoint, all target joints were resolved in all participants, all participants terminated prophylactic FVIII replacement therapy, and mean ABR dropped 96% from a baseline of 16.3 to 0.7 (median, 0 events). Mean annualized FVIII utilization (after week 5) declined from 136.7 infusions at baseline to 5.5 annualized infusions (median, 0 infusions) at the end of year three. In addition, health related quality of life captured using the Haemo-QoL-A,¹³ a validated disease specific quality of life instrument, demonstrated improvements in the mean total score and in each of the six domains at week 26, year 1, year 2 and year 3 respectively.¹⁴

Three-year efficacy outcomes from the Phase 1/2 study were further substantiated by preliminary 26-week data from the Phase 3 study.¹⁵ According to the more conservative CS assay, participants reached FVIII activity levels of moderate (one participant), mild (six participants), non-hemophilic (seven participants), and below level of quantification for the CS assay (two participants). By OS assay, all participants reached FVIII activity levels within ranges defined as moderate (two participants), mild (four participants), or non-hemophilic (ten participants). Overall, participants showed an 85% reduction in mean ABR and 95% reduction in mean annualized FVIII utilization after week 5.

Comparators: Appropriate comparison of valoctocogene roxaparvovec with medications most commonly used for prophylaxis in adults with severe hemophilia A, including emicizumab and FVIII therapies, will best approximate effects on patient outcomes and the health system. Of FVIII prophylaxis therapies, the most relevant comparator will be recombinant factor prophylaxis within adults with severe hemophilia A.

Dr. Steven Pearson

Re: Comments on “Valoctocogene Roxaparvovec and Emicizumab for Hemophilia A: Effectiveness and Value – Draft Background & Scope”

Recently reported prophylaxis utilization information in US adults with severe hemophilia A without inhibitors finds that the most commonly used prophylaxis medication classes are as follows (percentage by patient share):¹⁶ Standard half-life factor VIII products: 34.0%; Extended half-life factor VIII product: 27.8%; Emicizumab: 37.3%; Plasma-derived Factor VIII: 0.8%. These data suggest that the appropriate comparators for valoctocogene roxaparvovec include standard half-life FVIII products (Advate, Afstyla, Helixate, Kogenate, Kovaltry, NovoEight, Nuwiq, Recombinate, Xyntha), extended half-life FVIII products (Adynovate, Eloctate, Jivi), and emicizumab (Hemlibra). Standard half-life FVIII products, extended half-life FVIII products, and emicizumab account for about 99% of prophylaxis in severe adults with hemophilia A without inhibitors in the US.

We emphasize that similar patient populations should be used when evaluating valoctocogene roxaparvovec next to other investigational therapies and comparators. Importantly, this includes adult persons with severe hemophilia A using prophylaxis who are of similar age and weight. Importance is placed on similarity in weight because FVIII products, emicizumab, and valoctocogene roxaparvovec are prescribed according to weight-based dosing.

Outcomes: Inclusion of FVIII levels will help inform a comprehensive comparative assessment of valoctocogene roxaparvovec, given their predominant use as a surrogate outcome in the study of hemophilia treatments.

In addition to the outcomes proposed by ICER in the Draft Background and Scope, BioMarin recommends that FVIII activity level be included in the list of outcomes that may help determine efficacy, and how a patient feels, functions, and survives.

BioMarin agrees with ICER’s statement that “severity based on factor level does not perfectly correlate with actual clinical severity,” which is corroborated by a communication from the Scientific and Standardization Committee of the International Society of Thrombosis and Hemostasis that concludes residual FVIII activity level accounts for approximately 70% of clinical phenotype in hemophilia.¹⁷ Nonetheless, FVIII activity level was considered a core outcome for inclusion in hemophilia A gene therapy clinical trials by the coreHEM initiative, which comprised a multidisciplinary panel of patients, clinicians, researchers, drug developers, methodologists, regulators, health technology assessors and payers.¹⁸ Furthermore, there is a substantial body of evidence that demonstrates that individuals with severe hemophilia A, (FVIII activity <1 IU/dL) experience vastly different clinical morbidity than individuals living with moderate or mild forms of hemophilia A.¹⁹ For example, FVIII activity levels that fall into the mild range of hemophilia A (5-40 IU/dL) are associated with a reduced likelihood of spontaneous and subclinical joint bleeding,²⁰ which can lead to chronic and progressive arthropathy, pain, and limited mobility.²¹

BioMarin appreciates the opportunity to provide input on ICER’s draft clinical scope of valoctocogene roxaparvovec, particularly as it pertains to Population, Framework, Comparators, and Outcomes. Please contact me with questions or clarifications.

Sincerely,



Adrian Quartel, MD
Group Vice President, Head Global Medical Affairs
BioMarin Pharmaceutical Inc.

Dr. Steven Pearson

Re: Comments on “Valoctocogene Roxaparvovec and Emicizumab for Hemophilia A: Effectiveness and Value – Draft Background & Scope”

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February 13, 2020

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

Dear ICER Review Panel:

Genentech, a member of the Roche Group, appreciates the opportunity to provide comments on the *Valoctocogene Roxaparvovec and Emicizumab for Hemophilia A: Effectiveness and Value Draft Scope* [1]. We are dedicated to bringing system-wide solutions that lower costs for patients, while also sustaining innovation and ensuring patients have access to the medicines they need. This commitment to innovation led to the development of Hemlibra® (emicizumab-kxwh), the first new class of medicine in nearly 20 years for people with hemophilia A [2], approved for prophylaxis in persons ages newborn and older, with or without factor VIII (FVIII) inhibitors [3].

Leveraging our experience on the previous ICER emicizumab review and on our expertise in hemophilia A, we have three recommendations for this assessment:

- 1. To address unique uncertainties on the durability and predictability of effect of gene therapy, ICER should apply the “Single or Short-Term Transformative Therapies” methods adaptations, consult peer-reviewed literature, and integrate expert input.**
- 2. Due to differences in clinical trial designs and eligible patient populations, ICER should create separate cost-effectiveness models for emicizumab and valoctocogene roxaparvovec.**
- 3. ICER’s model of emicizumab should start at age zero to capture the totality of the disease burden over time and most accurately assess the value of this intervention.**

We further expand on these recommendations with supporting references and rationale below.

- 1. To address unique uncertainties on the durability and predictability of effect of gene therapy, ICER should apply the “Single or Short-Term Transformative Therapies” methods adaptations, consult peer-reviewed literature, and integrate expert input.**

We strongly recommend adapting the valoctocogene roxaparvovec model to account for the unknown duration of effect, as well as inter- and intra-patient variability in response [4-6]. In the Draft Scope, ICER proposes using a lifetime model, however, there is no mention of how the uncertainty regarding the duration of effect and other assumptions will be handled [1]. Gene therapy as a class of therapeutics is still in its infancy and durability over a lifetime is largely unknown. Therefore, assumptions such as a lifetime duration of response, even in the most optimistic scenarios, are not supported by available evidence. ICER acknowledges the limitations in the data including the small patient population who received valoctocogene roxaparvovec and a limited follow-up of three years [1,7]. Recently published literature modeled a slow decline in the treatment effect three years post valoctocogene roxaparvovec administration, with 10% of patients not responding from the onset [5,6]. Subsequent treatments for non-responders were also included [6]. We urge ICER to consider these assumptions, evaluate peer-reviewed literature, and work with

clinical experts to align on the most appropriate duration of treatment effect for valoctocogene roxaparvovec.

2. Due to differences in clinical trial designs and eligible patient populations, ICER should create separate cost-effectiveness models for emicizumab and valoctocogene roxaparvovec.

We strongly believe that independent evaluations need to be conducted due to several significant differences in the available data and outcomes as listed in **Table 1**. ICER indicated that, data permitting, emicizumab may be compared to valoctocogene roxaparvovec, as well as FVIII prophylaxis [1]. Unlike gene therapy, emicizumab is indicated for a broader patient population and is the only treatment approved for all hemophilia A. Given the anticipated indication for valoctocogene roxaparvovec (i.e., adults with hemophilia A without FVIII inhibitors), a combined economic analysis would be incomplete, as it could only be conducted in a subset of the emicizumab-eligible population [8]. Choosing FVIII prophylaxis as the sole comparator for each intervention independently will ensure the resulting analyses are comprehensive and scientifically rigorous.

Table 1. Key differences between emicizumab and valoctocogene roxaparvovec data

	Emicizumab	Valoctocogene roxaparvovec	Implications
Study population	<u>HAVEN 2, HOHOEMI [9,10]</u> -Pediatrics (<12 years) with hemophilia A, with and without inhibitors <u>HAVEN 1, 3, 4 [11-13]</u> -Adolescents and adults (≥12 years) with hemophilia A, with and without inhibitors	<u>Phase 1/2 and 3 [8,14]</u> -Adults (≥18 years) with hemophilia A -Excluded: people with hemophilia A with inhibitors (current and history of), pre-existing AAV-5 antibodies	-Disease trajectory varies by age group -Age is a strong risk factor for FVIII inhibitor development, a burdensome complication of hemophilia A [15,16] -Pediatric patients benefit from early prophylaxis treatment to preserve joint health [17]
Study design	<u>HAVEN 1, 3 [11,12]</u> -Randomized, open-label study comparing prophylaxis vs. no prophylaxis <u>HAVEN 2, 4, HOHOEMI [9,10,13]</u> -Non-randomized, open-label	<u>Phase 1/2 and 3 [8,14]</u> -Single-arm, open-label	-Differences in the study design do not allow for a scientifically rigorous comparison -The lack of a comparator arm for valoctocogene roxaparvovec limits the ability to indirectly compare the two interventions
Efficacy endpoints	<u>Primary</u> -Treated bleed rate at 24 weeks (annualized bleed rate) [3] <u>Secondary</u> -All bleeds, treated joint bleeds, treated spontaneous bleeds [3] -Intra-individual comparisons of bleeding rates ^{‡§} [9,11,12]	<u>Primary</u> -Dose required to achieve expression of FVIII at or above >5 IU/dL at 16 weeks [14] -Change in FVIII activity at 52 weeks [8] <u>Secondary</u> -Change in FVIII replacement utilization [8] -Change in annualized bleeding [‡] [8]	-Differences in the outcomes measured, and methodologies to assess these outcomes, do not allow for a scientific and rigorous comparison -The exact correlation between FVIII levels and the annual bleed rate is still unknown
[‡] Treated bleeds; [§] Intra-individual comparisons included only the participants who had been in the non-interventional study, which allowed for analyses of similar, prospectively collected data regarding bleeding events and medication in a cohort of participants who had received prophylaxis and emicizumab; [§] for pivotal studies HAVEN 1, 2, and 3			

3. ICER’s model of emicizumab should start at age zero to capture the totality of the disease burden over time and most accurately assess the value of this intervention.

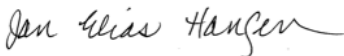
In the interest of further enhancing the scientific credibility of the emicizumab model, we request that ICER’s model of emicizumab accounts for the full disease trajectory by:

- beginning at age 0 years
- including the risk of FVIII inhibitor development
- including subsequent treatment after FVIII inhibitor development (i.e., emicizumab, bypassing agents, and immune tolerance induction)

The aforementioned recommendations are based on existing clinical guidelines, which recommend initiation of prophylaxis early in life to prevent joint damage and improve outcomes [17,18]. Emicizumab is approved for all people with hemophilia A, ages newborn and older, and does not enhance or induce FVIII inhibitor development [3]. Failing to include people <18 years, who can currently receive emicizumab, will limit the applicability and validity of the model. Moreover, FVIII inhibitors develop in childhood, at a median age of 3 years [15,17,19]. In addition to the above recommendations, we encourage ICER to be consistent in the description of patient populations to ensure clarity in the findings captured in future documents pertaining to this review (e.g., “hemophilia A without inhibitors to factor VIII” vs. “with hemophilia A”).

In closing, we are confident in the value that emicizumab brings to all people with hemophilia A. Genentech, in collaboration with clinical experts, has developed two models addressing assumptions and outcomes for emicizumab over a lifetime, which should be used as a foundation for this review [20-22]. We believe incorporating the recommendations above will result in a more objective and complete analysis of the interventions. We are open to sharing our health economic and clinical expertise in hemophilia A through active engagement with ICER in this review.

Sincerely,



Jan Elias Hansen, Ph.D.
Vice President, Evidence for Access Medical Unit
Genentech, US Medical Affairs

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Steven D. Pearson, MD, MSc, FRCP
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February 13th, 2020

IHASC Response to ICER Scoping Document

Dear Dr. Pearson,

This letter is in response to the recent ICER scoping document, *Valoctogene Roxaparvovec and Emicizumab for Hemophilia A: Effectiveness and Value*, published on January 24th, 2020. By way of introduction, we are the International Hemophilia Access Strategy Council (IHASC) – a multi-stakeholder group of HTA experts, health economists, physicians and patients. As part of this council, the HTA considerations subgroup looks to raise awareness to the unique situation of gene therapy in hemophilia and how assessments can be performed to understand the true value of these treatments. While this initiative is supported by Bayer, the company does not control the ideas or intellectual content coming out of the group.

By bringing together our diverse expertise, we work together towards the common goal of helping to ensure that innovative, evidence-based therapies for hemophilia can reach the patients that need them. We hope that by offering our unique multi-stakeholder perspective into the ICER scoping document, we can provide a useful contribution to the upcoming review of the first gene therapy in hemophilia A.

We are supportive of the following points that have been addressed in the recently published draft scoping document, arranged by PICOTS elements:

Populations

- ICER may want to consider how its stated population of focus, i.e., people with hemophilia A (of unspecified severity) without inhibitors to factor VIII, accords with the patient populations in the available clinical trial data, e.g., the AAV5-hFVIII-SQ trial, whose patients were adults with severe hemophilia A, apparently without inhibitors. The value of gene therapy is dependent on several factors including age, severity of the disease, individual attitudes to risk, and these should be included in the assessment to give information about which persons may benefit most from this option.

Interventions

- No additional comments.

Comparators

- As the proposed target population is focused on hemophilia A without inhibitors, we agree with the inclusion of FVIII prophylaxis as a comparator to gene therapy.

- The inclusion of emicizumab in the assessment is also supported, as the previous evaluation by ICER was conducted in patients with inhibitors to recombinant FVIII therapies. It needs to be determined whether emicizumab is cost-effective in a distinct assessment.
- In addition, prophylaxis regimes are providing different cost-effectiveness ratios, so an assessment should be undertaken on the relevant costs and outcome to use for this comparator⁷.

Outcomes

- We support the incorporation of relevant real-world data (RWD) in the value assessment. In the context of small sample sizes in trials of therapies for rare disease, compilation of RWD into real-world evidence (RWE) is useful to evaluate patient-relevant treatment effects due to the limitations of the patient population.
- The scoping document highlights several relevant outcomes that are consistent with a patient-centered value framework previously developed by IHASC,¹ including annual bleed rate (ABR), pain, HRQoL, and sustainability of health (e.g., joint preservation and lifelong productivity). Some additional endpoints that are worth including are musculoskeletal complications, inhibitor development (studies have indicated that gene therapies may enable patients to avoid the burdensome and costly development of inhibitors²), and FVIII expression levels (current treatment guidelines³ aim to maintain trough levels above 1 IU/dL whereas gene therapies seek to enable patients to consistently express higher levels of FVIII).
- Among the parameters used to define success of gene therapy are achieving FVIII expression at pre-defined levels, duration of maintaining a pre-defined level of FVIII expression, duration of preventing spontaneous bleeds regardless of expression levels, and the amount of time patients can avoid having to resume FVIII prophylaxis. Recently published cost-effectiveness models have conservatively used 90% of the pre-screened population achieving treatment success through the defined follow-up without the need to resume FVIII prophylaxis.^{4,5}
- The magnitude and duration of FVIII expression and other outcomes are uncertain to date, given the promising yet limited clinical trial data available thus far. Therefore, it is important to consider and appraise all available clinically relevant data, including from earlier phase 1 and 2 trials. This is appropriate so long as these studies have been conducted in the designated target population (i.e., hemophilia A without inhibitors), and considering potentially clinically relevant differences across subgroups with mild, moderate, and severe conditions as suggested above.
- Successful gene therapy will make it possible for an individual with hemophilia to live achieve the same health related quality of life as the normal population. The measurement of overall quality of life improvement is thus key to assessment of value. We suggest that ICER will rethink the choice of cost-effectiveness model based on bleeding episodes. As is seen from the two published evaluations, the choice of model and data have a significant impact on the result. (ref 5 and 6).
- Published cost-effectiveness studies of gene therapy use very different principles and data for costing alternatives. Both studies also show that the major driver of value is

the savings in costs of prophylaxis. A key determinant of value and thus a “reasonable price” are assumptions of future prices. We note that the scoping document does not discuss the issues involved^{8,9}.

Timing

- The efficacy of gene therapies in hemophilia is likely to persist longer than is covered by the clinical trial evidence published to date (e.g., longer than three-year follow-up).⁶ To improve certainty of findings regarding sustained factor expression and other outcomes, it is important to draw upon clinical trial results, further reports of longitudinal follow up of trial populations, and any other clinically relevant cohorts, as they become available. Such follow-up of clinical trial and real-world populations for longitudinal outcomes may prompt reassessment, as appropriate.

Settings

- No additional comments.

Other Aspects

Useful Study Designs

- Given the challenges of obtaining head-to-head comparative data (i.e., vs. prophylaxis with FVIII) in hemophilia, novel trial designs include observational run-in periods to enable pre-post comparisons. We recommend including data from the non-interventional run-in period of the phase 3 trial for BMN270. This will replicate real-world treatment while also capitalizing on the robust data-capturing methods of clinical trials that is typically not feasible in retrospective chart reviews.

Cost Offsets

- Where standard therapy for hemophilia in high-income countries can be expensive, gene therapy that is effective in expressing FVIII in indicated populations may yield enough cost offsets to be cost saving, even within several years post-treatment. In assessing value and budget impact, it will be important to monitor patient outcomes, relative costs of therapies and cost offsets, real-world patient access, and related market impacts over time.

We very much appreciate that ICER provides this opportunity to provide public input to the scoping document for *Valoctogene Roxaparvovec and Emicizumab for Hemophilia A: Effectiveness and Value*. We hope that our contribution will help to inform transparent, evidence-based assessments.

Sincerely,

IHASC HTA Considerations Subgroup
Clifford Goodman, Peter Neumann, and Bengt Jönsson

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February 13, 2020

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Re: ICER's Review of Valoctocogene Roxaparvovec (BioMarin Pharmaceutical, Inc) and Emicizumab (Genentech, Inc) for the Treatment of Hemophilia A.

To Whom It May Concern:

The National Hemophilia Foundation (NHF) and 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.

Thank you for the opportunity to provide comment to the Institute for Clinical and Economic Review (ICER) on the Draft Scoping Document for review of Valoctocogene Roxaparvovec (BioMarin Pharmaceutical, Inc.) and Emicizumab (Genentech, Inc) for the treatment of hemophilia A without inhibitors compared to Factor VIII (FVIII) replacement therapy. We are pleased to submit the following additional comments elaborating and expanding upon our initial submission during the open comment period.

Hemophilia and Gene Therapy

While ICER has familiarity with hemophilia given its prior work on Emicizumab for people with hemophilia and an inhibitor, it is important that it recognize the importance of the additional potential for a durable therapy such as gene therapy. Hemophilia treatment has undergone rapid technological advances over the past 60 years. Lifespan, with the notable and tragic exception of a decrease for individuals who were exposed to HIV- and HCV-tainted clotting factor products, has improved from less than 20 years in the 1950s to near normal. Unfortunately, however, morbidity and mortality persist despite rapid therapeutic advancements. For instance, prophylactic therapy delays but does not eliminate joint disease in affected individuals; optimal prophylactic protocols, moreover, remain undefined; and substantial barriers continue to impede universal adoption of prophylaxis in any event.¹

Because optimal treatment remains out of reach for so many, the idea of “curing” hemophilia has captured the imagination of patients, their caregivers, and their healthcare providers for decades. Based on the clinical trial results reported to date, the hemophilia patient community in 2020 appears to be closer to a treatment that may relieve them from the treatment burdens of ongoing prophylaxis and/or FVIII trough levels that place them at significant risk of bleeding when their circulating FVIII activity level drops below a therapeutic level. At the same time, safety remains paramount, especially given the community’s history with iatrogenic delivery of viral pathogens in plasma-derived concentrates, leading to widespread mortality. Patient concerns about eligibility for treatment, durability of therapy, the potential for post-administration bleeding, access to therapy, cost and cost-sharing burdens, etc., persist – but so does hope for improved treatment and quality of life.

¹ Srivastava A. Haemophilia Care – Beyond the Treatment Guidelines, Haemophilia 20:4-10. <https://doi.org/10.1111/hae.12429>

The only way that these questions will be fully resolved is through real-world experience and rigorous follow-up. While NHF and HFA remain strongly committed to vigilance in safety of the therapies upon which our community rely, the uncertainty surrounding gene therapy should be addressed through ensuring appropriate patient education, informed consent / shared decision making and longitudinal data collection. Waiting for certainty in each aspect is not in keeping with the goals of the 21st Century Cures Act, which was designed to help accelerate medical product development and bring new innovations and advances to patients who need them faster and more efficiently.

We were pleased to see the recent announcement within the new 2020-2023 Value Assessment Framework that ICER plans to review real-world evidence beginning 12 months and at 24 months post-review. While several of the outcomes discussed in this comment letter will be available for evaluation at the time of the initial review, we fully anticipate others will only be evident with additional time to collect data and real-world experience.

Selecting the Appropriate Value Framework

NHF and HFA encourage ICER to utilize the Value Framework for the Assessment of Treatment for Ultra-Rare Conditions and the Adapted Value Assessment Methods for High-Impact “Single Short-Term Therapies” (SST) for evaluation of Valoctocogene Roxaparvovec. Valoctocogene Roxaparvovec clearly fits within the criteria for their use.

- The treatment is envisaged for a patient population of fewer than 10,000 individuals – According to the latest data reported by the Centers for Disease Control and Prevention’s Community Counts program (March 2019)² – the national surveillance program for the bleeding disorders community – there are 19,192 PwHA (people with FVIII deficiency) of all ages registered within the U.S. Hemophilia Treatment Center network. Since gene therapy is unlikely to be licensed for use in children, PwHA under age 18 can be excluded from the total number, leaving <11,000 adult PwHA.³ This number includes PwHA with all levels of disease severity, and again, if adults with mild hemophilia are excluded, who are unlikely to be eligible for gene therapy, then the number of adults with moderate and severe hemophilia FVIII is approximately 6,700. Further reductions in the eligible patient population will occur due to pre-existing immunity to AAV5, prior history of an inhibitor, and/or significant liver disease, along with other exclusion criteria. This means that the target treatment population is well below the ultra-rare 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 – Due to the significant limitations noted, we do not envision a scenario where there would be more than 20,000 PwHA seeking use of Valoctocogene Roxaparvovec based on current disease prevalence and known anti-body estimates, described above. In addition, it would be inappropriate to assume that 100% of PwHA across all severities would aspire to use this treatment. Besides known restrictions, PwHA are genotypically and phenotypically unique, and bleeding frequency and severity will differ. PwHA vary, too, in their preferences and their assessments of the risk-benefit profile of novel treatments. Based on these data, it is clear there is little chance of a future expansion that would extend the target population above 20,000 individuals.
- The treatment potentially offers a major gain in improved quality of life and/or length of life – Valoctocogene Roxaparvovec has the potential to offer a major gain in improved quality of life and/or

² March 2019 HTC Population Profile. Centers for Disease Control and Prevention. Available at: <https://www.cdc.gov/ncbddd/hemophilia/communitycounts/data-reports/2019-3/index.html>.

³ Pasi KJ et al. Multiyear Follow-up of AAV5-hFVIII-SQ Gene Therapy for Hemophilia A. N Engl J Med. 2020 Jan 2;382(1):29-40. doi: [10.1056/NEJMoa1908490](https://doi.org/10.1056/NEJMoa1908490).

length of life for some PwHA. The published data, coupled with self-reported experiences received by NHF and HFA from participants in Valoctocogene Roxaparovec and related clinical trials, clearly demonstrate the potential for this new class of treatment to deliver a life-changing benefit.

- High-impact “single and short-term therapies” (SSTs) – Valoctocogene Roxaparovec meets the definition to be considered an SST. The therapy will be delivered through a single outpatient intervention and it is a treatment that offers a significant potential for substantial and sustained major health gain or halts the progression of hemophilia-related sequelae. Clinical trial results demonstrate these criteria have been met.³

We are unclear how ICER will conduct the analysis and apply the various value framework adaptations in the current review when one intervention (Valoctocogene Roxaparovec) is eligible for consideration under the ultra-rare and SST frameworks and the other (Emicizumab) will be evaluated under the traditional value framework. Due to the inherent limitations with gene therapy being utilized in some sub-populations (e.g., antibodies to the vector, age or other co-morbidities) the target population for the two therapies will be different. We seek your clarification in the Revised Scoping Document. This clarification will be particularly important in conducting the head-to-head comparison of Valoctocogene Roxaparovec and Emicizumab.

Interventions and Comparators

We support that ICER is planning to compare Valoctocogene Roxaparovec with both FVIII replacement therapy and Emicizumab, as well as Emicizumab with FVIII replacement therapy. We believe that it is important that ICER’s review reflect real-world conditions, patient economic burden, and clinical outcomes. At present, there is considerable real-world heterogeneity when it comes to the standard of care for PwHA. Some patients have gravitated to Emicizumab since its approval, while others (in conjunction with their doctors) have chosen to continue with clotting factor regimens. Against this background, it is appropriate for ICER to compare both interventions with factor replacement products and to each other.

Incorporation of Patient-Important Outcomes

In our previous letter submitted during the initial open input period, we commented on the importance of incorporating an updated set of patient-important outcomes within the PICOTS framework. Following our review of the Draft Scoping Document, we wish to elaborate and expand upon our initial comments.

Prophylaxis became the standard of care in recent decades due to the success of prophylactic therapy in preventing bleeding and decreasing the progression of joint disease. This in turn prompted investigators, treaters and regulators to adopt annualized bleeding rate (ABR) as the primary outcome in evaluating the efficacy of hemophilia treatments. But new hemophilia treatments, gene therapy and coagulation mimetics (e.g. Emicizumab), produce unprecedented results in terms of level of durability of their clotting effect. As a result, a reassessment of outcomes measured is required, in order to ensure an appropriate measure of the value contributed by these advanced therapies.⁴ This necessity has also been noted by the FDA in the agency’s recent guidance document on hemophilia gene therapy, “Although ABR is a direct assessment of clinical benefit, ABR has limitations in that it is a relatively infrequent event in patients on prophylactic factor regimens and the decision

⁴ Konkle BA, Johnsen JM, Wheeler M, Watson C, Skinner M, Pierce GF; My Life Our Future programme. Genotypes, phenotypes and whole genome sequence: Approaches from the my life our future haemophilia project. *Haemophilia*. 2018;24(Suppl. 6):87-94. doi: 10.1111/hae.13506

by a patient to treat a possible bleeding episode is usually somewhat subjective. For these reasons, more objective endpoints, such as factor activity levels, are desirable.”⁵

The outcomes of interest listed in the Draft Scoping Document remain highly relevant and appropriate. However, for ICER to achieve a complete evaluation of gene therapy and to differentiate and distinguish between gene therapy, mimetics and standard replacement therapy, we recommend the following refinements and enhancements.

We renew our request that ICER utilize the core outcome set established through coreHEM (Table 1), an international multi-stakeholder project to develop a core outcome set for clinical trials of gene therapy in hemophilia, in its methodology and evaluation.⁶ Participating experts and stakeholders included patients, clinicians, payers, health technology assessment groups, regulators, life sciences companies and others. coreHEM produced the first set of guidelines recommending a specific, minimum set of outcomes to include in hemophilia gene therapy clinical trials. The coreHEM project was jointly led by the Green Park Collaborative (GPC), the National Hemophilia Foundation (NHF), and McMaster University.

Utilization of an established core outcome set will ensure that patient perspectives on critical outcomes are included in the analysis, allow fair comparisons between alternative treatments, and allow more accurate assessments of the value of these novel therapies relative to standard of care.

Table 1 Core outcome set for hemophilia gene therapy trials.

coreHEM Core Outcome Set			
	<i>Outcome</i>	<i>Domain</i>	<i>Definition</i>
Core Outcome Set	<i>Frequency of bleeds</i>	Physiological/Clinical	How often a person with hemophilia experiences a bleed (e.g. the annualized bleeding rate)
	<i>Factor activity level</i>	Physiological/Clinical	The amount of factor VIII (Hemophilia A) or factor IX (Hemophilia B) activity measured in the blood.
	<i>Duration of expression</i>	Physiological/Clinical	How long after the gene therapy treatment the expression of FVIII or FIX lasts; the length of time that the heightened factor activity level is maintained.
	<i>Chronic pain</i>	Pain/Discomfort	The presence of persistent pain that can last for a long time, such as over months or longer, including the frequency, intensity, duration and character of the pain
	<i>Utilization of healthcare system (direct costs)</i>	Resource Use	Measures of uses and related costs incurred from the need for healthcare and treatment associated with hemophilia, including days in hospital, hospital readmissions, emergency room visits, bleeds, inhibitors, factor VIII/IX infusion, bypass agent use, pain and other medications, home health/homecare services, specialist consultations, and professional caregivers
	<i>Mental health</i>	Emotional Functioning	A person’s psychological status; whether a person has positive feelings (joy, excitement, ease of living, new outlook on life) or negative feelings (anxiety, depression, fear, uncertainty) associated with having hemophilia or the treatment of hemophilia. Can be related to the act of making an irreversible treatment decision or the effect of the gene therapy in curing one’s hemophilia.

⁵ Human Gene Therapy for Hemophilia Guidance for Industry. U.S. Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research January 2020. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/human-gene-therapy-hemophilia>. Last accessed February 10, 2020.

⁶ Iorio A, Skinner MW, Clearfield E, et al. ; for the coreHEM panel. Core outcome set for gene therapy in haemophilia: Results of the coreHEM multistakeholder project. Haemophilia. 2018;24:e167–e172. doi: 10.1111/hae.13504

We request ICER update and expand the list of outcomes to include factor activity level, chronic pain, and mental health when evaluating gene therapy.

- **Factor Activity Level** – Today, factor activity level remains the driver of clinical decision making. Linking factor activity level to clinical outcomes will be an important consideration for this and future evaluations of novel therapies. In keeping with the coreHEM guidelines, NHF and HFA encourage ICER not to rely solely on annualized bleed rate as the criterion for evaluation of hemophilia gene therapy. A multi-factorial decision approach which also includes factor activity level, treatment burden and quality of life factors is essential.⁷ We wish to call ICER’s attention to the following discussion from the coreHEM manuscript, *“Of the six core outcomes, only frequency of bleeds is a “legacy” outcome, consistently used in past haemophilia trials; its inclusion in the core will enable comparing efficacy and effectiveness with existing treatment and also calculating derived measures such as impact on target joints, a surrogate endpoint for long-term joint function deterioration. Achieved factor activity level (i.e. restoration of lacking clotting capacity) was the single measure required for approval in the early era of haemophilia treatment, but was later eclipsed by outcomes geared to show the clinical impact of achieving minimal factor activity levels with prophylactic treatment. With gene therapy achieving near-normal factor activity levels, measurement of factor levels is being actively discussed⁸ and may well re-emerge as a relevant outcome for regulatory approval, in line with the [21st Century Cures Act] principles⁸.”*⁶
- **Chronic Pain** – While the list of proposed outcomes included within the PICOTS framework includes pain, we wish to highlight the importance of not looking at pain generally, but the differential between acute and chronic pain should be evaluated. The two types of pain manifests differently. A patient has chronic pain when they report pain for more than three months. Pain may be intermittent or continuous, and may be of variable intensity over this time. This is pain not associated with an acute bleeding episode. coreHEM recognizes that pain should be assessed based upon how it affects function⁹. Pain in response to a bleeding event and pain resulting from a lifetime of bleeding leading to chronic arthropathy are different in the way they occur and interfere with quality of life.
- **Mental Health** – The proposed PICOTS include some elements of this coreHEM-specified mental health outcome (e.g., anxiety, depression, and overall well-being), but these elements individually will not capture the potentially transformative nature of achieving a sustained therapeutic response through a single short-term intervention. Evaluation should not be limited to the presence or absence of anxiety or depression, but rather should also weigh the transformational change that a PwHA might experience, whether positive or negative. Evaluating the “life interference” of living with hemophilia would be a more appropriate metric. At present, a specific patient reported outcome (PRO) instrument does not exist, but work has been initiated to develop and validate a new instrument. In the interim, we would refer ICER to the work of the coreHEM Mental Health project for guidance on the current thinking of experts in the field for metrics which could be included within the ICER evaluation.¹⁰

Where data are not available for the outcomes of interest (those listed in the Draft Scoping Document and the additional outcomes noted above) or a metric is not yet established, ICER should nevertheless recognize the full set of outcomes within its valuation as they are of importance to patients. Such recognition will guide future

⁷ Pierce, G.F., Ragni, M.V., van den, Berg, H.M., Weill, A., O’Mahony, B., Skinner, M.W. and Pipe, S.W. (2017), Establishing the appropriate primary endpoint in haemophilia gene therapy pivotal studies. *Haemophilia*, 23: 643-644. [doi:10.1111/hae.13313](https://doi.org/10.1111/hae.13313)

⁸ Gottlieb S. Implementation of the 21st Century Cures Act: Progress and the Path Forward for Medical Innovation. Testimony of Scott Gottlieb, M.D. Commissioner of Food and Drugs Administration Before the Committee on Health, Education, Labor & Pensions, U.S. Senate.

⁹ coreHEM: Developing Comparative Effectiveness Outcomes for Gene Therapy in Hemophilia Final Report. May 21, 2018. Version 1. Available at: <http://www.cmtptnet.org/green-park-collaborative/core-outcome-set-initiatives/corehem/>. Last accessed February 10, 2020.

¹⁰ Green Park Collaborative and the National Hemophilia Foundation launch project to develop a PROM to measure mental health outlook. January 29, 2020. Available at: <http://www.cmtptnet.org/news-room/view/project-to-develop-a-prom-to-measure-mental-health-outlook/>. Last Accessed February 10, 2020.

clinical trials and the planned real-world evaluations noted in the 2020-2023 ICER Value Assessment Framework. Additionally, sponsors should be requested to provide data which could quantify the relationship between steady-state factor activity levels and bleeding outcomes when available⁵. This will help meet the data need identified by FDA and validate factor activity level as a surrogate endpoint.

NHF and HFA further caution that, while numerous generic and disease-specific PRO instruments exist, there is no standard approach or uniformity in their use. During a December 2018 FDA workshop on Product Development in Hemophilia, panelists representing the patient perspective emphasized that PROs in use today are not content relevant for contemporary outcomes of importance to patients given the numerous treatment advances since their development. An improved and validated hemophilia-specific PRO which was recently developed using both content experts and persons living with hemophilia can be found in the Patient Reported Outcomes, Burdens and Experiences (PROBE) project. The PROBE questionnaire is comprised of four major sections (demographic data, general health problems, hemophilia-related health problems and health-related quality of life).^{11,12} We would be pleased to offer ICER relevant data from the PROBE study for use within this evaluation.

HFA, too, has made patient-driven, patient-centered efforts to engage community members as key participants in research projects. In 2017, HFA launched a patient-reported outcomes research registry. This registry is a platform HFA uses to collect data for research on the bleeding disorders community to more effectively serve the needs of bleeding disorder patients and their families.

Finally, NHF and HFA solicited data from the community in 2014 when FDA held a Patient Focused Drug Development Initiative (PFDD) meeting on hemophilia and other bleeding disorders. These data were included in the Voice of the Patient report released by the Agency following the meeting.¹³ The report emphasizes our patients' concerns about the pain, anxiety and depression they experience associated with their bleeding disorder. We encourage you to reference this report as you consider novel treatments for hemophilia and other bleeding disorders.

Adverse Events

In addition to updating the list of outcomes of interest, we also suggest ICER consider reviewing the coreHEM core outcome set for an updated list of adverse event of interest within gene therapy.^{6,9} Adverse events that were rated as critically important by the coreHEM group and/or by patients were categorized as three domains: short-term adverse events (liver toxicity, short term immune response to FVIII/FIX, immune response to gene therapy, thrombosis), long-term adverse events (development of other disorders, vector integration into host genome, duration of vector-neutralizing response) and mortality.

Potential Other Benefits and Contextual Considerations

There are several other elements which will be important for ICER to consider in its evaluation.

¹¹ Chai-Adisaksopha C, Skinner MW, Curtis R, et al Psychometric properties of the Patient Reported Outcomes, Burdens and Experiences (PROBE) questionnaire BMJ Open 2018;8:e021900. doi: [10.1136/bmjopen-2018-021900](https://doi.org/10.1136/bmjopen-2018-021900)

¹² Skinner, M. W., Chai-Adisaksopha, C., Curtis, R., Frick, N., Nichol M., Noone, D., O'Mahony, B., Page, P., Stonebraker, J. S. and Iorio, A. (2018). The Patient Reported Outcomes, Burdens and Experiences (PROBE) Project: development and evaluation of a questionnaire assessing patient reported outcomes in people with haemophilia. Pilot and Feasibility Studies, 2018 4:58. doi: [10.1186/s40814-018-0253-0](https://doi.org/10.1186/s40814-018-0253-0).

¹³ Report of The Voice of the Patient. Hemophilia A, Hemophilia B, von Willebrand Disease and Other Heritable Bleeding Disorders meeting. May 2016. U.S. FDA Patient-Focused Drug Development Initiative.

<https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM513311.pdf>. Last Accessed February 11, 2020.

An important patient consideration will be the expected durability of treatment and sustained FVII level post gene therapy. When modeling for durability, we encourage ICER to consider scenario analysis that looks to a lifetime horizon as well as a shorter duration based upon results in the published literature. The potential to avoid or interrupt sequelae associated with living with severe hemophilia A will be deemed of benefit to many patients, even if that benefit is not lifelong.

Other patients will be most concerned with uncertainty, e.g., the unknown ability to re-treat with the same or a different gene therapy vector if the initial response is less than optimal due to the formation of antibodies to the initial vector. While we can anticipate science will overcome this hurdle in time, it remains, for the time being, an important patient consideration.

Also, we know that 30% of severe PwHA develop inhibitory antibodies to FVIII at some point in their lifetime.¹⁴ While the hypothesis is not yet proven, when considering the value of Emicizumab vs prophylaxis with FVIII replacement therapy, ICER may wish to consider the potential savings associated with a delay or avoidance of inhibitor formation.

Conclusion

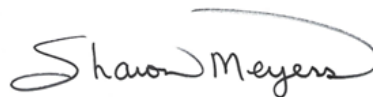
We conclude, as we started, by reminding ICER of hemophilia's complexity. The disease and treatment burdens associated with the disorder; the variations among patients; and the potential rewards and risks of any novel therapy – all these considerations demand an individualized, patient-centric approach to treatment. Patients and doctors should have the opportunity to select the treatment that meets patients' individual goals, physiology, life circumstances, and risk-benefit assessment. There will be PwHA who will eagerly adopt these potentially transformative novel therapies at their earliest opportunity - and other PwHA who, for equally important reasons, hold back. All must have access to the clinically appropriate therapies that best serve their needs and treatment goals.

We appreciate the opportunity to provide these comments and thank you for your consideration. We look forward to continuing to work with ICER as you undertake this review.

Sincerely,



S. Dawn Rotellini
Interim Chief Executive Officer
National Hemophilia Foundation



Sharon Meyers, M.S., CFRE
President & CEO
Hemophilia Federation of America

¹⁴ Witmer, Char, and Guy Young. "Factor VIII inhibitors in hemophilia A: rationale and latest evidence." *Therapeutic advances in hematology* vol. 4,1 (2013): 59-72. [doi:10.1177/2040620712464509](https://doi.org/10.1177/2040620712464509)

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February 13, 2019

**NOVO NORDISK PUBLIC RESPONSE TO ICER DRAFT SCOPING DOCUMENT:
*Valoctocogene Roxaparvovec and Emicizumab for Hemophilia A: Effectiveness and Value***

Novo Nordisk appreciates the opportunity to participate in ICER's review of valoctocogene roxaparvovec and emicizumab for hemophilia A. New and innovative treatments for hemophilia are advancing patient care, and the adoption of preventive regimens for hemophilia have transformed a debilitating disease with long-term orthopedic consequences into a more manageable chronic condition for most patients. The ultimate goal for the treatment of patients with hemophilia A is to maintain high factor VIII levels and subsequently minimize bleeding, and therefore avoid the development of joint damage. This goal can be achieved with valoctocogene roxaparvovec, emicizumab, and factor VIII replacement therapy; therefore, all three treatments should be available to patients for the foreseeable future.

One of the keys to success in the progression of the treatment paradigm in hemophilia has been maintaining the ability of patients, together with their hemophilia treaters, to consider the best treatment modality and regimen for their individual needs, challenges, and lifestyles. The efficacy of each treatment varies across patients, and patients will have different preferences in terms of their hemophilia treatment; therefore, options are essential to ensure the most successful care for each patient.

Novo Nordisk would like to highlight certain considerations for the scope of ICER's review:

RECOMMENDATIONS

1. Consider focusing the analysis and discussion primarily on efficacy and safety.

Although we agree that the cost-effectiveness and budget impacts of new treatments are important, these outcomes should not be the primary outcomes of interest in a value framework intended to evaluate the effectiveness and value of valoctocogene roxaparvovec and emicizumab. The cost-effectiveness or budget impact results alone may not adequately represent the clinical benefits of prophylactic treatments in hemophilia A, due to the fact that the cost of hemophilia treatment, regardless of outcome, has been found to be the primary healthcare cost driver in hemophilia patients.¹⁻³ As ICER is an organization centered on clinical and economic review, and this review focuses on three very different treatment modalities with variable levels of long-term evidence, efficacy and safety should be at the forefront of this review as central considerations in the proposed value framework and weighted appropriately in the model. In addition, the well-established measures of clinical efficacy and safety should be separate from the measures of clinical benefit (pain, health related quality of life, burden of treatment) proposed by patient organizations.

Patients with hemophilia A and their physicians ultimately choose which treatment is best suited for them. ICER can help provide guidance to this process by focusing on clinical efficacy and safety outcomes, which are initially the most important outcomes. Prophylaxis with currently available factor VIII replacement therapies has been shown to achieve low bleeding rates with a proven safety profile. Therefore, newer treatment options should demonstrate at least similar levels of safety and efficacy to be viable alternatives to current therapies. The cost-effectiveness and budget impact results can be supportive measures used to guide payers and physicians on the economic value of multiple treatment options relative to each other. Patients and their physicians can then use this in addition to other measures of clinical benefit to finalize their treatment decisions.

All three treatment types in this review have unique merits, but the extent of available data on demonstrated efficacy and safety varies with each modality and may also be dependent on the severity of disease in the studied patient cohorts. Importantly, there is a paucity of real-world efficacy and safety data for valoctocogene roxaparvovec. Although a consensus on the outcomes for gene therapy trials, supported by NHF, was recently published,⁴ the data on these outcomes has yet to be collected and evaluated. In addition, emicizumab has only been available to patients in the United States for approximately 1 year, limiting the evaluation of long-term safety and efficacy data. The limited duration for which mortality data has been available for these treatments is also to be noted as it adds uncertainty to the impact these treatments have on patient mortality.

2. The value in the key measures of clinical benefit identified in the draft analytical framework (Fig 2, page 4 of draft scoping document) lies in assisting patients and physicians with the establishment of individualized treatment plans.

Patients will ultimately use these secondary outcomes to determine the best therapy for their individual needs, which can be a daunting task, considering all of the current treatment options. These secondary outcomes, such as burden of treatment, pain, and quality of life, should also be considered in the review, but not included in the value framework so as to not potentially confound the value associated with standard measures of efficacy and safety. In terms of data on these clinical benefits, there is essentially no real-world data for gene therapy and little long-term real-world data for emicizumab due to its recent entry into the hemophilia treatment space. These secondary outcomes should be studied in more depth before they are included in a value framework.

3. Although economic modeling is more useful looking at a long-term time horizon, due to the currently available clinical data in this evaluation, a more limited time horizon should be considered for the health economic models, especially for gene therapy.

The long-term clinical trial data for valoctocogene roxaparvovec will be unavailable for years, and thus far, there is some uncertainty around its long-term efficacy and safety, which could potentially impact the medium-term treatment costs as well as costs related to long-term outcomes. Importantly, it is unclear if factor VIII expression in these patients will remain at “normal” levels; therefore, the durability of this treatment is questionable. Also, the effectiveness of repeated gene therapy interventions after initial exposure to AAV is uncertain, and additional therapies, including factor replacement therapy, may be required to control and prevent bleeds once effectiveness decreases. Long-term safety also remains uncertain; there is evidence that AAV vectors for gene therapy may be linked to an increased cancer risk.⁵

When considering emicizumab, there is a documented risk of neutralizing anti-drug antibodies developing and reducing its efficacy at preventing bleeds;⁶ therefore, an analysis based on a shorter time frame may also be relevant. Variability in patient response could lead to break through bleeds, which would require treatment with factor VIII replacement products.

Additionally, consideration should be given to conducting sensitivity analyses around the longevity of the clinical efficacy in gene therapy and neutralizing antibody development for emicizumab. Specifically, the cost associated with initiating agents to treat break-through bleeding, such as factor VIII or bypass agents.

CONCLUSION

Novo Nordisk would like to thank ICER for their consideration of our response. In summary, valoctocogene roxaparvec, emicizumab, and factor VIII replacement products have unique clinical profiles and should all be treatment options for patients with hemophilia A. Given the limited availability of data for valoctocogene roxaparvec on the key clinical benefits identified in the draft analytical framework, a better reflection of value may be focused on efficacy and safety. In addition, the time horizon for the health economic models should be limited, as the long-term efficacy and safety of both valoctocogene roxaparvec and emicizumab remain unclear.

We look forward to the analysis and appreciate the opportunity to provide feedback.



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February 13, 2020

Steven D. Pearson, M.D., M.Sc.

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RE: Takeda Response to the Draft Background and Scope for the Institute for Clinical and Economic Review (ICER) Evaluation to Assess Gene Therapy for Hemophilia A

Dear Dr. Pearson:

Takeda appreciates the opportunity to provide comments during this open period regarding the planned evaluation to assess gene therapy for hemophilia A.

Takeda Pharmaceutical Company Limited (Takeda) is a global, value-based, R&D-driven biopharmaceutical leader, committed to bringing better health and a brighter future to patients by translating science into highly innovative medicines. At Takeda, our commitment and expertise in bleeding disorders run deep. Expanding upon an unparalleled heritage built over 70 years, Takeda provides more life-changing and life-saving medicines to those with bleeding disorders than any other company. Our broad portfolio of transformative medicines is backed by decades of real-world experience, providing trusted and effective treatments to manage a variety of bleeding disorders.

Given ICER's ongoing evaluation of gene therapy in hemophilia A, Takeda would like to contribute to the development of a solid modeling framework and use of the most relevant data. Takeda concurs with ICER in proposing prophylaxis with factor VIII preparations as a comparator of interest when assessing gene therapy in hemophilia A and emicizumab, therefore, Takeda presents important information for ICER's consideration regarding the review of the draft scoping document.

1. Use of all bleeds as the primary endpoint

The goal for prophylaxis for hemophilia A is to prevent all spontaneous bleeds^{1,2,3,4,5} because even a single bleed may become life-threatening or contribute to permanent joint disease.^{3,6,7} If the final scope were to focus on just "treated bleeds" or other secondary bleeding based endpoints, ICER would, by default, inadvertently ignore non-treated or other non-reported bleeds, where such consequences, long term outcomes, and associated costs are unknown. **Given this, Takeda agrees with ICER for listing "rates of bleeding events" first in the draft scoping document and assumes ICER intends to examine the rate of ALL bleeds in the review as a primary focus.**

2. Breakthrough bleeding and the need for factor VIII concentrates

All breakthrough bleeds should be treated urgently^{1,8} to prevent bleed exacerbation and long-term detrimental effects, including debilitating joint arthropathy.⁸ Factor VIII concentrates are a mainstay

of patient management in hemophilia A, as they are the only approved treatment for surgery^{9,10} and breakthrough bleeds,¹¹ which can occur regardless of prophylactic regimen.^{12,13,14,15} In clinical trials assessing emicizumab prophylaxis, ~50–71% of patients experienced ≥ 1 breakthrough bleed, and factor VIII concentrate was co-administered in >50% of patients (breakthrough bleeds, surgery, bleed prevention).^{14, 15, 25} Since factor VIII concentrates play an essential part in hemophilia A treatment in patients on regular emicizumab prophylaxis, **Takeda recommends that breakthrough bleeding and the associated on-demand factor VIII concentrate costs should also be included in both intervention arms as listed in the draft scoping document.**

3. Cost considerations: Drug acquisition and cost methodology

Drug price is a cornerstone of any health technology appraisal. It is a significant input, and the chosen methodology should be carefully considered. Cost accounting in hemophilia A is complex and consists of significant discounts, often realized by both public and private payers. **Takeda suggests that ICER use reported average sales price (ASP) as the base case net-price input into its model and not merely the ASP Limit published by Centers for Medicare & Medicaid Services (CMS).**^{16,17,18} In hemophilia, “reported ASP” (calculated as CMS ASP Payment Limit net of the additional 6% and \$0.226/IU clotting factor furnishing fee) is more reflective of real-world reimbursement practices as it places market forces on contracting within the supply chain, and the overall price paid outside of Medicare covered patients. For example, state-based Medicaid programs cover up to 25.7% of the patients with hemophilia A, and largely have implemented actual acquisition costs (AAC) based reimbursement methods where reported ASP (not the ASP limit) more closely reflects actual provider reimbursement.¹⁹

Additionally, payors reimburse for the dispensed volume of products which can be different in the real-world than weight-based dosing prescribed. Dispensed volume in the real-world can be influenced by patient adherence and drug wastage (i.e. the difference between weight-based prescribed dose and actual number of vials dispensed). **Takeda encourages ICER to incorporate real-world dispensed volumes to account for adherence and wastage in their net-price drug pricing models.**

Takeda welcomes the opportunity to work with ICER to develop the most accurate model and real-world net-price inputs for included interventions and comparators.

4. Prophylaxis with factor VIII preparations: Standard half-life (SHL) vs. Extended half-life (EHL)

Careful consideration of all relevant facts associated with the use of SHL and EHL concentrates must be examined. Some relevant facts are:

- **Differences in market utilization:** The use of EHL factor VIII concentrates in the prophylactic setting shows an increasing trend since 2014, from 1.2% to 21.2% in 2018²⁰ (please note report produced before emicizumab approval in non-inhibitor patients). Despite the EHL market growth, the utilization of SHL concentrates in 2018 reached 78.7% of the

total market.²⁰

- **Differences in dosing in prophylactic setting:** Takeda’s recombinant factor VIII concentrate portfolio includes both SHL and EHL products for hemophilia A. When ADVATE® (Antihemophilic Factor [Recombinant]), a SHL concentrate, is given as prophylaxis, the indicated dose is 20 to 40 IU per kg every other day (3 to 4 times weekly).²¹ In contrast, ADYNOVATE® (Antihemophilic Factor [Recombinant], PEGylated), an EHL concentrate, is given as prophylaxis at a dose of 40-50 IU per kg body weight 2 times a week in ages 12 and older (for ages <12 years, at a dose of 55 IU per kg body weight 2 times a week).²¹

The differences mentioned above in addition to unit prices and other factors lead to material differences in real-world prophylaxis rates, patient medication adherence, and outcomes.²² **Takeda recommends ICER to carefully consider the several nuances between EHLs and SHLs in an attempt to aggregate the “factor FVIII preparations” group as listed in the draft scoping document. At the minimum, Takeda recommends ICER should appropriately weigh the differences in unit price, dosing, and outcomes between EHLs and SHLs as it attempts to aggregate the category.**

Takeda also suggests adding the definition of “prophylactic treatment” in the ICER draft background and scope document. This would ensure the data in the model would be the prophylactic use of factor VIII rather than on-demand use of factor VIII in the prophylactic setting and avoid any confusion between on-demand and prophylaxis uses of factor VIII. Treatment in the prophylactic setting is defined as “regularly scheduled treatments, administered 2 or 3 predetermined days of the week, starting at an early age (before frequent bleeds have occurred) to prevent bleeding”.²³ Following this definition, **the base case in the final scoping document should not be based on previous episodic therapy with factor VIII, i.e., on demand.** On-demand preparations are not a standard of care in severe phenotypes.²⁴

Takeda appreciates the opportunity to participate in this scientific dialogue while ICER conducts its assessment of therapies for hemophilia A. As leaders in the hemophilia and bleeding disorder field, the consideration above can help lead to a better scientific approach.

Kind Regards,

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