May 23, 2022

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

Re: Response to the Institute for Clinical and Economic Review's draft scoping document for the clinical and economic assessment of valoctocogene roxaparvovec

Dear Dr. Pearson:

On behalf of BioMarin, I appreciate the opportunity to provide comment on the Institute for Clinical and Economic Review (ICER)'s *Draft Background and Scope* for *Gene Therapy for Hemophilia B and an Update on Gene Therapy for Hemophilia A*, posted on May 5, 2022. The purpose of this letter is to provide input in the context of valoctocogene roxaparvovec, an investigational therapy for hemophilia A.

We agree with ICER's proposals to use adaptations of the *ICER Value Framework for treatments of serious, ultra-rare conditions* and the *ICER Value Framework for treatments of high-impact "single and short term therapies" (SSTs)* for the assessment of this one-time gene therapy for severe hemophilia A.

BioMarin would like to provide three recommendations relating to the scope of the review in the sections headlined below.

Comparators

Recommendation: Data for comparators should reflect a patient population similar to the one studied in valoctocogene roxaparvovec clinical trials. Clinical and economic data for the most representative FVIII and emicizumab prophylaxis regimens should reflect contemporary real-world practices in the United States.

The patient population eligible for valoctocogene roxaparvovec comprises adults with severe hemophilia A without inhibitors, who are currently managed with the most clinically appropriate standard of care. Recent reports suggest emicizumab, standard half-life (SHL) FVIII products and extended half-life (EHL) FVIII products made up >95% of treatments in a similar population. These data indicate that the appropriate comparators for valoctocogene roxaparvovec are emicizumab, SHL FVIII, and EHL FVIII products.

One of the key findings from ICER's last review is that dosing of FVIII prophylaxis products in current practice is much higher than in clinical trials, which has significant implications for the clinical and economic review of valoctocogene roxaparvovec. Studies of real-world prescription patterns in recent years confirm a dose range similar to inputs provided by the American Thrombosis and Hemostasis Networks (ATHN) used by ICER in the last assessment.[1-4] BioMarin would like to emphasize the importance of using dosing and utilization patterns reflective of the current practices for both FVIII prophylaxis and emicizumab in this review and recommends that ICER consults again with ATHN, the largest network of hemophilia treatment centers, to obtain the latest real-world utilization data for this updated evaluation.

Outcomes

Recommendation: The treatment benefit of valoctocogene roxaparvovec should be assessed in the context of plasma FVIII levels, hemostatic control, and FVIII utilization. Data from the phase 1/2 and phase 3 (GENEr8-1) trials have consistently demonstrated durable and sustained bleeding control and low FVIII utilization, even at lower levels of FVIII activity.

BioMarin agrees with ICER that factor level is not in itself a patient-important outcome, although it is an important surrogate or intermediate outcome that can provide valuable information on treatment efficacy. While previous modeling with epidemiologic data suggests that a FVIII activity level >15 IU/dL is protective against joint bleeding, even low levels of clotting factors reduce bleeding.[5] In GENEr8-1, within their most recent year of follow-up 77% of participants with FVIII levels in the range 3-5 IU/dL by chromogenic substrate assay and 28% of those with FVIII <3 IU/dL by chromogenic substrate assay reported no bleeds requiring treatment.[6] These data demonstrate that endogenous, transgene-derived FVIII activity at a lower level can be associated with sustained prevention of bleeding.

Regarding FVIII utilization, none of the 134 study participants in GENEr8-1 resumed prophylaxis within the first year after valoctocogene roxaparvovec administration. Six participants subsequently resumed prophylaxis (one to emicizumab and five to FVIII treatment) as of the most recent data cut-off with at least 2 years of follow-up for the entire cohort and at least 3 years for a subset of patients (N=17); all had at least one FVIII activity measure <5 IU/dL using one-stage assay prior to doing so.[6] In the phase 1/2 trial, none of the 7 participants dosed with 6E13 vg/kg had resumed prophylaxis as of their 5-year follow-up visit.[7]

Please also note that BioMarin intends to offer an Outcomes-Based Agreement for valoctocogene roxaparvovec. We are currently in discussions with payers to design and implement the Agreement. The details and specific criteria have not been finalized, but BioMarin anticipates that the terms and structure will be similar to the program evaluated as part of the last assessment.

Comparative value analysis

Recommendation: Broad and consistent improvement in patient-reported quality of life beyond bleeding control and freedom from repeated prophylaxis administration warrants a health utility increment for patients treated with valoctocogene roxaparvovec.

In ICER's draft scope for evaluating valoctocogene roxaparvovec gene therapy for hemophilia A, the proposed economic model structure considers four mutually exclusive bleed states, as well as lifetime risk and consequences of arthropathy. However, these health states do not capture the impact of hemophilia on participation (i.e., the ability to participate in family life, recreational activities, school activities, and work activities), which ICER acknowledges is the outcome that matters most to patients.

GENEr8-1 has demonstrated broad and consistent improvements in health-related quality of life sustained through 2 years post gene transfer.[8] More importantly, the observed quality-of-life improvements are independent from reductions in bleeding. For example, similar to those who experienced a reduction in annualized bleeding rate (ABR) following valoctocogene roxaparvovec administration, participants with no change in ABR (ABR of zero before and after gene transfer) and those who had an increased ABR after gene transfer also reported improvement in quality of

life. Measured by the Hemophilia-specific Quality of Life Questionnaire for Adults, clinically meaningful improvements were reported in the domains *Role Functioning*, *Consequence of Bleeding*, *Worry*, and *Treatment Concern*. Additionally, the Hemophilia Activities List assessment tool revealed that the largest activity-related improvement was in the area of leisure activities and sports, while the Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questionnaire: Hemophilia Specific assessment tool showed less classroom and work impairment after gene transfer.

During 2+ years of follow-up in GENEr8-1, a single dose of valoctocogene roxaparvovec achieved a higher degree of hemostatic control than that achieved after a mean of 135.9 doses of FVIII infusions per year while on prior prophylaxis.[6] As frequent intravenous infusions are an enormous burden to patients and their caregivers, the ability to eliminate the need for routine prophylaxis, with its associated compliance and access issues, needs to be quantitively factored into the economic model.

As hemophilia is a lifelong disorder with interrelated clinical and patient-reported outcomes that are influenced by many factors, including activity level, worry, frequency of treatment, and access to healthcare, BioMarin encourages ICER to include a utility increment for patients treated with valoctocogene roxaparvovec. Such adjustment would reflect the unique benefits to patients and families that clinical trials have shown are achievable with valoctocogene roxaparvovec, which in a single administration offers the prospect of steady-state factor levels well above what is feasible with existing therapies.

Thank you again for the opportunity to provide input as ICER finalizes the scope for the reassessment of the clinical and economic value of valoctocogene roxaparvovec for hemophilia A. Please do not hesitate to contact me with any questions or clarifications.

Sincerely,

Wing Yen Wong, MD
Group Vice President, Head of Global Medical Affairs
BioMarin Pharmaceutical Inc.

References

1. Croteau SE, Cheng D, Cohen AJ, Holmes CE, Malec LM, Silvey M, et al. Regional variation and cost implications of prescribed extended half-life factor concentrates among U.S. Haemophilia Treatment Centres for patients with moderate and severe haemophilia. Haemophilia. 2019;25(4):668-75.
2. Recht M, He C, Chen E, Cheng D, Solari P, Hinds D. Resource utilization and treatment costs of patients with severe hemophilia A: Real-world data from the ATHNdataset. eJHaem. 2022:1-12.
3. Rind DM, Walton SM, Agboola F, Herron-Smith S, Quach D, Chapman R, et al. Valoctocogene Roxaparvovec and Emicizumab for Hemophilia A without Inhibitors: Effectiveness and Value. Final Report. Boston, MA: Institute for Clinical and Economic Review; 2020. Updated November 20, 2020. Available from: https://icer.org/wp-content/uploads/2020/10/ICER_Hemophilia-A_Final-Report_112020.pdf.
4. Kenet G, Chen YC, Lowe G, Percy C, Tran H, von Drygalski A, et al. Real-world rates of bleeding, factor VIII use, and quality of life in individuals with severe haemophilia A receiving prophylaxis in a prospective, noninterventional study. J Clin Med. 2021;10(24):5959.
5. Den Uijl IE, Mauser Bunschoten EP, Roosendaal G, Schutgens RE, Biesma DH, Grobbee DE, et al. Clinical severity of haemophilia A: does the classification of the 1950s still stand? Haemophilia. 2011;17(6):849-53.
6. Mahlangu J, Ozelo CM, Peyvandi F, et al. Efficacy and safety of valoctocogene roxaparvovec gene transfer for severe hemophilia A: Results from the GENEr8-1 year two analysis [Oral presentation]. 15th Annual Congress of the European Association for Haemophilia and Allied Disorders (EAHAD); February 2-4, 2022; Virtual.
7. Pasi KJ, Laffan M, Rangarajan S, Robinson TM, Mitchell N, Lester W, et al. Persistence of haemostatic response following gene therapy with valoctocogene roxaparvovec in severe haemophilia A. Haemophilia. 2021;27(6):947-56.
8. Dunn A. Health-related quality of life over 2 years following valoctocogene roxaparvovec adeno-associated virus gene transfer for severe haemophilia A: Results from GENEr8-1 [Oral presentation]. World Federation of Hemophilia (WFH) 2022 World Congress, May 8-11; Montreal, QC, Canada.

May 25, 2022

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

Re: Comments on "Gene Therapy for Hemophilia B and an Update on Gene Therapy for Hemophilia A – Draft Background & Scope"

Dear ICER Review Panel:

CSL Behring appreciates this opportunity to comment on the Institute for Clinical & Economic Review (ICER)'s draft scoping document for the assessment of the gene therapy product etranacogene dezaparvovec (EtranaDez) for hemophilia B. CSL Behring welcomes ICER's efforts to model the breadth of clinical and economic benefits that rare disease gene therapies – including EtranaDez – can provide to patients, caregivers, the healthcare system, and society as a whole. This letter provides input on ICER's May 5, 2022, document "Gene Therapy for Hemophilia B and an Update on Gene Therapy for Hemophilia A – Draft Background & Scope".[1] Our comments focus exclusively on the evaluation of EtranaDez for Hemophilia B, and comments pertain to Framework, Comparative Efficacy, and Model Perspective.

Framework: Given the rarity of Hemophilia B and the characteristics of EtranaDez as a gene therapy, we agree with ICER that evaluation using both the Ultra-Rare and the Single or Short-Term Therapies (SST) frameworks is most appropriate.

CSL Behring appreciates that ICER is considering evaluating EtranaDez under both the ultra-rare disease[2] and SST[3] frameworks. CSL Behring agrees with ICER's scope document that these frameworks are appropriate and reiterates that these frameworks would be best suited for evaluation of EtranaDez.

The ultra-rare disease framework by ICER lists in its most recent criteria that the framework will be used when: "*An eligible patient population for the treatment indication(s) included in the scope of the ICER review is estimated at fewer than approximately 10,000 individuals*." and "*There are no ongoing or planned clinical trials of the treatment for a patient population greater than approximately 10,000 individuals*."[2] Estimates for the total Hemophilia B patient population in the United States are less than 6,000 which is well below the ultra-rare population definition of 10,000.[4] Furthermore, we note that the proposed label for EtranaDez would include only those either already using FIX replacement therapy prophylactically or those with a history of serious bleeding episodes, excluding the majority of Hemophilia B patients.[5]Finally, to our knowledge, no clinical trials have ever been performed in moderately-severe to severe Hemophilia B with greater than 1,000 individuals.[6] Therefore, the rare disease threshold is certainly met by the patient population intended for EtranaDez, with a total population of less than half of the ultra-rare population definition.

The criteria for consideration of the SST framework state that this framework will apply for: "*therapies that are delivered through a single intervention or a short-term course of treatment that demonstrate a significant potential for substantial and sustained health benefits extending throughout patients' lifetimes*."[3] As a gene therapy, EtranaDez fits the criteria of being a therapy

administered as a single intervention, as EtranaDez is administered as a single intravenous infusion.[5] Recently, data from the HOPE-B Phase 3 clinical study of EtranaDez demonstrated that eighteen months after receiving a single infusion of $2x10^{13}$ gc/kg dose of Etranacogene dezaparvovec, participants had a 64% reduction in annualized bleed rate (ABR) compared with a six month lead-in on only rFIX prophylaxis ($P = 0.0002$).[7] Furthermore, circulating FIX levels increased from less than 2 IU/dL at baseline to 39.0 IU/dL at 6 months ($P < 0.0001$) and 36.9 IU/dL at 18 months ($P < 0.0001$), suggesting strong sustained improvement.[7] Patient quality of life as measured by the Haem-A-QoL survey improved in every domain.[7] Therefore, EtranaDez offers a substantial health benefit. Shortly, 24-month data from HOPE-B will be available which we anticipate will reinforce the durability of response. Data from both Phase 2b study, and from the Phase I/II study with a predecessor therapy (AMT-060, wild type FIX gene), support that EtranaDez offers a durable response. The Phase I/II study showed patients exhibited sustained FIX level (7.2% at year 5 vs 7.1% at year 1), 99% reduction in rFIX consumption and a 0.0 ABR at five years in the five patients who were dosed with AMT-060 at $2x10^{13}$ gc/kg.[8] [8] In addition, CSL Behring will be generating additional modelling data to elucidate the potential long term expression of FIX activity following EtranaDez administration. Therefore, EtranaDez offers a substantial and sustained health benefit that may to extend for many years and is suitable to be evaluated under the SST framework, as has been assumed by ICER.

Comparative Efficacy: The HOPE-B trial is the best source of comparative efficacy between EtranaDez and FIX prophylaxis

In the draft scoping document, ICER notes: "*We will compare etranacogene dezaparvovec to prophylaxis using factor IX preparations*".[1] We agree wholeheartedly with this approach, as the patient population of interest would require prophylaxis as opposed to simply treating on-demand and no other treatment options currently exist for moderately severe to severe hemophilia B patients.[6] ICER further notes: "*Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes*". Here, we note that while no multi-arm head-to-head trials exist for EtranaDez, the HOPE-B trial was designed with a lead-in phase where patients were monitored on routine prophylaxis for at least six months.[7] This is by far the most robust evidence base to draw upon to compare EtranaDez to FIX prophylaxis as patients serve as their own controls. Issues of heterogeneity of treatment effect modifiers and prognostic factors between trials is far less of a concern using this study design, and the lead-in prophylaxis period serves as the best comparative evidence between EtranaDez and FIX prophylaxis to use for economic evaluation. CSL Behring has also generated both matched-adjusted indirect comparisons between EtranaDez and Alprolix and Refixia and an inverse probability of treatment weighting (IPTW) analysis between EtranaDez and IDELVION that we can provide to ICER which corroborate these analyses. These data are preferable to naïve indirect comparisons and reinforce the robustness of EtranaDez's clinical benefits.

Perspective: A societal co-base case is appropriate given that EtranaDez is likely to produce a substantial benefit in patient productivity

ICER notes: "*In addition, a modified societal perspective will be explored in a scenario analysis, as data allow. This modified societal perspective analysis will be considered as a co-*

base case if the societal costs of care are large relative to direct health care costs, and the impact of treatment on these costs is substantial."[1]

CSL Behring agrees with ICER's plan to explore a societal perspective. Here, we note that a societal perspective is an appropriate co-base case, given that we anticipate that EtranaDez will have a substantial benefit on patient productivity which will translate into cost savings. First, we note that there is direct evidence that patients find that EtranaDez enables greater work and school functioning, as the HOPE-B trial found that there was a substantial improvement in the work/school domain of the Haem-A-QoL instrument (28.78%, $P = 0.0036$).[7] Furthermore, results from HOPE-B demonstrate that the prolonged effect of gene therapy enables patients to transition from moderately severe to severe FIX levels to mild hemophilia B at 18 months.[7] Hemophilia B poses a substantial impediment to patients realizing their full potential at work/school, with 95% of hemophilia B patients reporting that their disease has a negative impact on their employment.[9] Furthermore, the indirect costs of Hemophilia B have been shown to be nearly twice as high in patients with severe disease compared with mild/moderate ($8,421 annually per-person vs $4,416 annually per person).[10] The vast majority of these indirect costs are due to patients being unemployed or only partially employed as a consequence of their hemophilia B.[10] Given that EtranaDez is capable of significantly increasing patients' Factor IX levels and decreasing their annualized bleed rates to levels associated with patients with mild hemophilia B, and has directly demonstrated benefits in patient surveys of work well-being, CSL Behring considers it appropriate to use a societal perspective co-base case and agrees with ICER's strategy to explore this analytical framework to fully quantify the benefits of this gene therapy.

CSL Behring is grateful to have the chance to give input on ICER's draft clinical scope of EtranaDez, particularly as it pertains to Framework, Comparative Efficacy, and Perspective. Please contact us with questions or clarifications.

Sincerely,
Robert R. Rouse,
Head of US Market Access
CSL Behring Inc.

Reference List

[1]ICER (2022). *Gene Therapy for Hemophilia B and an Update on Gene Therapy for Hemophilia A: Draft Background and Scope*. Available online at: https://icer.org/wp-content/uploads/2022/05/ICER_Hemophilia_Draft-Scoping-Document_050522.pdf. Accessed: May 24, 2022.

[2]ICER (2020). *Modifications to the ICER value assessment framework for treatments for ultra-rare diseases*. Available online at: https://icerorg.wpengine.com/wp-content/uploads/2020/10/ICER_URD_Framework_Adapt_013120.pdf. Accessed: May 24, 2022.

[3]ICER (2019). *Adapted Value Assessment Methods for High-Impact "Single and Short-Term Therapies" (SSTs)*. Available online at: https://icerorg.wpengine.com/wp-content/uploads/2020/10/ICER_SST_FinalAdaptations_111219-1.pdf. Accessed: May 24, 2022.

[4]Soucie JM, Miller CH, Dupervil B, Le B, Buckner TW (2020) Occurrence rates of haemophilia among males in the United States based on surveillance conducted in specialized haemophilia treatment centres. *Haemophilia* 26 (3): 487-493.

[5]CSL Behring (2022). *HOPE-B: Trial of AMT-061 in Severe or Moderately Severe Hemophilia B Patients*. Available online at: https://clinicaltrials.gov/ct2/show/NCT03569891. Accessed: May 24, 2022.

[6]Davis J, Yan S, Matsushita T, Alberio L, Bassett P et al. (2019) Systematic review and analysis of efficacy of recombinant factor IX products for prophylactic treatment of hemophilia B in comparison with rIX-FP. *J Med Econ* 22 (10): 1014-1021.

[7]Miesbach W, Leebeek FWG, Recht M, Keye NS, Lattimore S et al. (2022) Final Analysis from the Pivotal Phase 3 HOPE-B Gene Therapy Trial: Stable Steady-State Efficacy and Safety of Etranacogene Dezaparvovec in Adults with Severe or Moderately Severe Haemophilia B. (#https://www.uniqure.com/EAHAD-2022-HOPE-B%20Oral%20presentation.pdf) *European Association for Haemophilia and Allied Disorders*. Virtual Conference, February 4, 2022.

[8]Miesbach W, Meijer K, Coppens M, Kampmann P, Klamroth R et al. (2021) Five Year Data Confirms Stable FIX Expression and Sustained Reductions in Bleeding and Factor IX Use Following AMT-060 Gene Therapy in Adults with Severe or Moderate-severe Hemophilia B. (#OC 26.3) *International Society on Thrombosis and Haemostasis (ISTH) 2021*. Virtual, Virtual. July 21, 2021.

[9]Cutter S, Molter D, Dunn S, Hunter S, Peltier S et al. (2017) Impact of mild to severe hemophilia on education and work by US men, women, and caregivers of children with hemophilia B: The Bridging Hemophilia B Experiences, Results and Opportunities into Solutions (B-HERO-S) study. *Eur J Haematol* 98 Suppl 86 18-24.

[10]Chen CX, Baker JR, Nichol MB (2017) Economic Burden of Illness among Persons with Hemophilia B from HUGS Vb: Examining the Association of Severity and Treatment Regimens with Costs and Annual Bleed Rates. *Value Health* 20 (8): 1074-1082.

Genentech
A Member of the Roche Group

May 27, 2022

Dear ICER Review Panel:

Genentech, a member of the Roche Group, appreciates the opportunity to provide comments on *Gene Therapy for Hemophilia B and an Update on Gene Therapy for Hemophilia A Draft Background and Scope* [1]. Hemlibra® (emicizumab-kxwh) is approved for prophylaxis to prevent or reduce the frequency of bleeding episodes in persons with hemophilia A (PwHA), ages newborn and older, with or without factor VIII (FVIII) inhibitors [2]. We are confident in the life-changing value that emicizumab has brought to PwHA and remain committed to ensuring that patients have access to the therapies that are best suited for their needs.

For this update of the 2020 assessment titled "*Valoctocogene Roxaparvovec and Emicizumab for Hemophilia A without Inhibitors: Effectiveness and Value*" [3], we urge ICER to ensure information on emicizumab, and any other chosen comparators, is fully updated to reflect the totality of relevant evidence for available prophylaxis treatments for PwHA.

Additionally, we have three key recommendations for the scope of this assessment:

1. **The value of valoctocogene roxaparvovec should be assessed based upon the GENEr8-1 trial, which involves comparison to FVIII products that are currently used for prophylaxis in PwHA.**
2. **Given major differences in the target populations, any comparison between valoctocogene roxaparvovec and emicizumab would be incomplete and potentially misleading.**
3. **Within the value assessment framework for single and short-term therapies, the valoctocogene roxaparvovec cure fraction along with the need for additional therapies should be taken into account.**

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

1. **The value of valoctocogene roxaparvovec should be assessed based upon the GENEr8-1 trial, which involves comparison to FVIII products that are currently used for prophylaxis in PwHA.**

Rationale: Bleeds in PwHA are often self-identified and self-treated. Within-subject comparison provides the most appropriate comparator arm for a valid scientific assessment. In fact, the Food and Drug Administration recommends this approach to assessing the annualized bleeding rate (ABR) when manufacturers design hemophilia gene therapy trials, given the enrolled patients should be on optimized prophylactic regimens [4]. Prior to treatment with valoctocogene roxaparvovec, each patient in the GENEr8-1 trial received FVIII prophylaxis for at least one year [5]. Thus, deriving the relative treatment efficacy from the GENEr8-1 trial provides a robust dataset to enable a more accurate clinical and economic assessment.

Additionally, standards for prophylactic regimens have evolved over time. Therefore, the GENEr8-1 trial represents more contemporary and relevant data on FVIII usage (including a mix of standard and extended half-life products), and outcomes for the target population of interest [5]. Use of within-subject comparisons to assess the relative treatment efficacy would be the more accurate approach than indirect comparisons across the different historical FVIII trials.

Implications/Recommendation: A direct comparison will result in more robust conclusions about the relative value of valoctocogene roxaparvovec. The findings will enable healthcare decision makers to better contextualize the clinical and cost-effectiveness profile of valoctocogene roxaparvovec versus FVIII.

2. Given major differences in the target populations, any comparison between valoctocogene roxaparvovec and emicizumab would be incomplete and potentially misleading.

Rationale: The treatment landscape for PwHA is complex and requires nuanced, yet evidence-based, treatment decisions that consider multiple factors such as bleeding risk, history of immune tolerance induction, joint bleeding history, comorbidities that impact the efficacy and safety of treatment, as well as preference and lifestyle choices. Emicizumab is the most commonly utilized form of bleeding prophylaxis for hemophilia A, followed by various standard and extended half-life FVIII replacement products [6].

However, as authors of the GENEr8-1 Trial stated, "efficacy of valoctocogene roxaparvovec cannot be directly compared with that of emicizumab [5]." Important differences in the clinical trial inclusion criteria that impact bleeding risk, as well as the differences in patients' capacity to benefit from therapy, preclude a comprehensive formal comparison for the following reasons:

First, the emicizumab target population is broad [2]. The emicizumab population includes adult and pediatric males and females with mild, moderate, or severe disease, patients with and without FVIII inhibitors, and individuals with a number of comorbidities including hepatitis C infection and/or HIV [2]. In contrast, the target population for valoctocogene roxaparvovec is highly selected, limited to adult males with severe hemophilia A without FVIII inhibitors, and without HIV or HCV [3].

Second, even when focusing specifically on PwHA without FVIII inhibitors, the baseline clinical characteristics of patients were different. For example, among patients in the GENEr8-1 trial, 28% had one or more "problem joints" (n= 37 of 132) [5]. However, in the HAVEN 3 study, 41% had one or more target joints (n = 26 of 63) [7].

Unfortunately, the underlying clinical differences in the trial populations, particularly the impact of bleeding risk, as well as the response to treatment, are not explicit. Bleeding risk associated with liver dysfunction/disease [8,9] and HIV [10-12] are clinically complex. These differences in baseline bleeding *risk* across the populations cannot simply be adjusted by the reported baseline annualized bleeding *rate*. The increased bleeding risk due to these comorbidities is further compounded by related changes in pharmacokinetics and impairments in drug metabolism [10,12,13].

Finally, as evidenced through real-world data, patients receiving emicizumab are more likely to have clinically complex disease [14]. A recent claims analysis found that relative to PwHA receiving prophylactic FVIII therapy, clinicians have channeled refractory PwHA to receive prophylaxis with emicizumab instead of (or subsequent to) other therapies.

In total, these differences in the target patient populations reflect variation in the capacity to benefit from either therapy. Such differences in these patient populations cannot adequately be controlled for with advanced statistical methods. Should ICER include emicizumab as a comparator, we recommend presenting comprehensive clinical information on the costs and benefits for its target population (all PwHA). A qualitative summary of important differences between the target populations and clinical evidence for emicizumab relative to valoctocogene roxaparvovec should accompany such information. This summary should center on the totality of real-world and clinical evidence on emicizumab and not on hypothesized performance in the narrow target population eligible for valoctocogene roxaparvovec. As many users of ICER reports may focus heavily on point estimates from cost-effectiveness modeling without complete understanding of uncertainty and limitations, we further caution that emicizumab should not be used as a comparator to valoctocogene roxaparvovec.

Implications/Recommendation: Major - and clinically important - differences in target populations and imbalanced bleeding risk across clinical trial populations for emicizumab and valoctocogene roxaparvovec make indirect comparisons incomplete and potentially misleading. As a result, healthcare decision makers may interpret the findings on comparative value in a way that could negatively influence patients' access to their therapies.

3. **Within the value assessment framework for single and short-term therapies, the valoctocogene roxaparvovec cure fraction along with the need for additional therapies should be taken into account.**

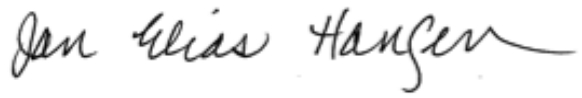
Rationale: Results of the GENEr8-1 trial showed that 15% (n=20 of 132) of patients remained "cured" at Week 104 (i.e., FVIII levels in the normal range), 24% (n=21) had FVIII levels in the moderate to severe disease range, and 5% (n=6) re-initiated prophylactic therapy with FVIII replacement products [15]. Additionally, 10% (n=13) of patients had a higher ABR after valoctocogene roxaparvovec treatment compared to before gene therapy was initiated. Over the two-year period, there was a gradual decline in the average (SD) FVIII levels, which were 43 (46) at 49-52 weeks, and 27 (32) at 106 weeks, indicating limited durability of treatment effect in this trial. Therefore, it is likely that patients will need active monitoring and follow up, as well as additional therapies.

Moreover, in addition to FVIII used to treat break-through bleeds, patients on long-term prophylaxis, as well as gene therapy, may require additional FVIII replacement for a variety of reasons (e.g., pre-surgery) that may impact total cost of care. For example, real-world evidence demonstrates that patients receiving emicizumab prophylaxis require an average (SD) of 3 (4) claims for FVIII replacement product per year [16]. Whereas, patients receiving FVIII prophylaxis have an average of 14 (12) claims per year [17].

***Implications/Recommendation**:* Not including up-to-date information on the cure fraction, durability of treatment effect, and need for additional therapies concomitantly with valoctocogene roxaparvovec could lead to overestimation of the benefits and underestimation of its costs.

In closing, emicizumab continues to deliver value as a transformative therapy in PwHA. We remain committed to generating robust evidence on the impact of emicizumab on patients and their families, as well as the healthcare system. In addition to the HAVEN 1-7 trials of emicizumab for PwHA [7,18-23], Genentech and other researchers continue to generate real-world evidence on related effectiveness [24-30], adherence and persistence [16,31,32], as well as healthcare resource use and costs [33,34] through numerous real-world studies. Incorporating the recommendations above would result in a more objective and informative assessment of valoctocogene roxaparvovec and its comparators. We thank you for this opportunity to share our health economic and clinical expertise about hemophilia A by actively engaging with ICER throughout this review.

Sincerely,



Jan Elias Hansen, PhD.
Vice President, Evidence for Access Medical Unit
US Medical Affairs, Genentech, Inc.

References

1. Institute for Clinical and Economic Review. Gene Therapy for Hemophilia B and an Update on Gene Therapy for Hemophilia A Draft Background and Scope. May 2022; Available at: www.icer.org. Accessed on May 16, 2022.
2. Genentech USA, Inc., A Member of the Roche Group. Hemlibra® (emicizumab-kxwh) injection for subcutaneous use prescribing information. December 2021; Available at: http://www.gene.com/download/pdf/hemlibra_prescribing.pdf.
3. Rind DM, Walton SM, Agboola F, et al. Valoctocogene Roxaparvovec and Emicizumab for Hemophilia A: Effectiveness and Value; Evidence Report. Institute for Clinical and Economic Review, October 16, 2020. https://icerreview.org/material/hemophilia-a-update-evidence-report/.
4. Food and Drug Administration (Center for Biologics Evaluation and Research) Guidance for Industry. Human Gene Therapy for Hemophilia. Docket Number: FDA 2018-D-2238. January 2020. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/human-gene-therapy-hemophilia. Accessed on May 25, 2022.
5. Ozelo MC, Mahlangu J, Pasi KJ, et al. Valoctocogene Roxaparvovec Gene Therapy for Hemophilia A. N Engl J Med. Mar 17 2022;386(11):1013-1025. https://www.ncbi.nlm.nih.gov/pubmed/35294811
6. Khairnar R, Decker-Palmer M, Mellor J, et al. Improvement in Annualized Bleed Rate in Patients with Hemophilia A Initiating Emicizumab-Physician Reported Outcomes from the Adelphi Hemophilia a Disease Specific Programme. Blood. 2021 Nov 23;138:1961.
7. Mahlangu J, Oldenburg J, Paz-Priel I, et al. Emicizumab Prophylaxis in Patients Who Have Hemophilia A without Inhibitors. N Engl J Med. Aug 30 2018;379(9):811-822. https://www.ncbi.nlm.nih.gov/pubmed/30157389
8. Shah NL, Northup PG, Caldwell SH. A clinical survey of bleeding, thrombosis, and blood product use in decompensated cirrhosis patients. Ann Hepatol. Sep-Oct 2012;11(5):686-690. https://www.ncbi.nlm.nih.gov/pubmed/22947530
9. Intagliata N, Shah NL. Hemostatic abnormalities in patients with liver disease. www.uptodate.com © 2022 UpToDate, Inc.
10. Wilde JT, Lee CA, Collins P, Giangrande PL, Winter M, Shiach CR. Increased bleeding associated with protease inhibitor therapy in HIV-positive patients with bleeding disorders. Br J Haematol. Dec 1999;107(3):556-559. https://www.ncbi.nlm.nih.gov/pubmed/10583257
11. Gandhi RT, Aboulafia DM. HIV associated cytopenias. www.uptodate.com © 2022 UpToDate, Inc.
12. Stanworth SJ, Bolton MJ, Hay CR, Shiach CR. Increased bleeding in HIV-positive haemophiliacs treated with antiretroviral protease inhibitors. Haemophilia. Mar 1998;4(2):109-114. https://www.ncbi.nlm.nih.gov/pubmed/9873848
13. Zgheib NK, Branch RA. Drug metabolism and liver disease: a drug–gene–environment interaction. Drug Metabolism Reviews. 2017 Jan 2;49(1):35-55.
14. Mahajerin A, Faghmous I, Kuebler P, et al. Channeling effects in the prescription of new therapies: the case of emicizumab for hemophilia A. Journal of Comparative Effectiveness Research.0(0):null. https://www.futuremedicine.com/doi/abs/10.2217/cer-2021-0278

15. Mahlangu et al. Efficacy and Safety of Valoctocogene Roxaparvovec Gene Transfer for Severe Hemophilia A: Results from the GENER8-1, Two-Year Analysis. 2022 EAHAD abstract presentation.
16. Khairnar et al. Real-world Persistence with and Adherence to Emicizumab Prophylaxis in People with Hemophilia A – Results from Two Secondary Claims Database Analyses. 2022. Presented at the World Hemophilia Federation.
17. Croteau SE, Cook K, Sheikh L, Chawla A, Sammon J, Solari P, Kim B, Hinds D, Thornburg CD. Health care resource utilization and costs among adult patients with hemophilia A on factor VIII prophylaxis: an administrative claims analysis. Journal of Managed Care & Specialty Pharmacy. 2021 Mar;27(3):316-26.
18. Oldenburg J, Levy GG. Emicizumab Prophylaxis in Hemophilia A with Inhibitors. N Engl J Med. 2017;377(22):2194-2195. https://www.ncbi.nlm.nih.gov/pubmed/29171814
19. Pipe SW, Shima M, Lehle M, et al. Efficacy, safety, and pharmacokinetics of emicizumab prophylaxis given every 4 weeks in people with haemophilia A (HAVEN 4): a multicentre, open-label, non-randomised phase 3 study. Lancet Haematol. Jun 2019;6(6):e295-e305. https://www.ncbi.nlm.nih.gov/pubmed/31003963
20. Young G, Liesner R, Chang T, et al. A multicenter, open-label, phase 3 study of emicizumab prophylaxis in children with hemophilia A with inhibitors. Blood. E-pub Date: 2019. DOI # 10.1182/blood.2019001869.
21. Clinicaltrials.gov. A Study to Evaluate the Safety, Efficacy, Pharmacokinetics and Pharmacodynamics of Emicizumab in Participants With Mild or Moderate Hemophilia A Without FVIII Inhibitors (HAVEN 6). Identifier: NCT04158648. Available at: https://clinicaltrials.gov/ct2/show/NCT04158648. Accessed on: May 26, 2022.
22. Clinicaltrials.gov. A Study to Evaluate the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Subcutaneous Emicizumab in Participants From Birth to 12 Months of Age With Hemophilia A Without Inhibitors (HAVEN 7). Identifier: NCT04431726. Available at: https://clinicaltrials.gov/ct2/show/NCT04431726. Accessed on: May 26, 2022.
23. Clinicaltrials.gov. Efficacy, Safety, and Pharmacokinetic Study of Prophylactic Emicizumab Versus No Prophylaxis in Hemophilia A Participants (HAVEN 5). Identifier: NCT03315455. Available at: https://clinicaltrials.gov/ct2/show/NCT03315455. Accessed on: May 26, 2022.
24. McCary I, Guelcher C, Kuhn J, et al. Real-world use of emicizumab in patients with haemophilia A: bleeding outcomes and surgical procedures. Haemophilia. 2020 Jul;26(4):631-6.
25. Ebbert PT, Xavier F, Seaman CD, Ragni MV. Emicizumab prophylaxis in patients with haemophilia A with and without inhibitors. Haemophilia. 2020 Jan;26(1):41-6.
26. Barg AA, Budnik I, Avishai E, et al. Emicizumab prophylaxis: Prospective longitudinal real-world follow-up and monitoring. Haemophilia. 2021; 27: 383- 391.
27. Barg AA, Livnat T, Budnik I, et al. Emicizumab treatment and monitoring in a paediatric cohort: real-world data. Br J Haematol. 2020; 191: 282- 290.
28. Levy-Mendelovich S, Brutman-Barazani T, Budnik I, et al. Real-World Data on Bleeding Patterns of Hemophilia A Patients Treated with Emicizumab. J Clin Med. 2021; 10: 4303.

29. Misgav M, Brutman-Barazani T, Budnik I, et al. Emicizumab prophylaxis in haemophilia patients older than 50 years with cardiovascular risk factors: Real-world data. Haemophilia. 2021; 27: 253- 260.
30. Hassan E, Jonathan L, Jayashree M. Real-world experience on the tolerability and safety of emicizumab prophylaxis in paediatric patients with severe haemophilia A with and without FVIII inhibitors. Haemophilia. 2021; 27:e698-e703.
31. Buckner T, Rapacchietta O, Hill D, et al. Improved Prophylaxis Adherence After Switching to Emicizumab: Real-World Data from a Single Center. Presented at the International Society on Thorombosis and Haemostasis. 2020. Abstract PB0937. Available at: https://abstracts.isth.org/abstract/improved-prophylaxis-adherence-after-switching-to-emicizumab-real-world-data-from-a-single-center/.
32. Hussain A, Thompson A, Divney A, et al. Retrospective review of Hemophilia patients before and after treatment with Emicizumab. Presented at the National Hemophilia Foundation 2020. Available at: https://www.hemophilia.org/research/research-projects/retrospective-review-of-hemophilia-patients-before-and-after-treatment-with-emicizumab.
33. Samelson-Jones BJ, Guelcher C, Kuhn J, et al. Real-world cost estimates of initiating emicizumab in US patients with haemophilia A. Haemophilia. 2021;27(4):591-598. https://onlinelibrary.wiley.com/doi/abs/10.1111/hae.14347
34. Mahajerin A, Khairnar R, Meyer C, et al. Changes in Healthcare Resource Use and Costs after Emicizumab Initiation for Hemophilia A. Presented at the Academy of Managed Care Pharmacy (AMCP) Nexus 2020. Available at: https://2020.amcpnexus.org/.

May 25, 2022

Submitted electronically to: Mfrederick@icer.org
Steven D. Pearson, MD, MSc
Institute for Clinical and Economic Review (ICER)
14 Beacon Street, 8th Floor
Boston, Massachusetts 02108

RE: ICER's Draft Background and Scope Document for Hemophilia A and B

Dear Dr. Pearson:

Novo Nordisk (henceforth referred to as "NN") is a global healthcare company committed to helping improve the lives of people with hemophilia A and B. NN's commitment to hemophilia research is demonstrated by a diverse portfolio of FDA-approved and investigational recombinant therapies. Among the FDA-approved medicines, NN offers two factor VIII therapies for prophylactic and/or on-demand treatment for hemophilia A[1,2], one factor IX therapy for on-demand treatment for hemophilia B[3], and one factor VIIa therapy for the treatment of bleeding episodes among patients with hemophilia A or B with inhibitors[4]. Moreover, NN is currently investigating a number of non-factor hemophilia treatments that have the potential to improve care for patients across hemophilia A and B with or without inhibitors.

Given NN's deep and storied commitment to improving the lives of patients with hemophilia, NN appreciates the opportunity to provide comments to ICER regarding the Hemophilia A and B Draft Background and Scope document released on May 5, 2022. We strive for an evidence-driven approach for this evaluation. After careful review of the draft scope, NN appreciates the opportunity to offer comments on the following: (1) product availability for all existing and innovative therapies, and (2) disaggregation of economic model comparators.

ICER should consider the importance of maintaining a product environment for patients, including existing and innovative therapies for hemophilia

In the Draft Background and Scope document, ICER announced its intention to evaluate two gene therapies (valoctocogene roxaparvovec, etranacogene dezaparvovec) in separate comparative clinical and cost-effectiveness analyses for hemophilia A and B, respectively. In its assessment, ICER will compare (1) valoctocogene roxaparvovec to prophylaxis using emicizumab and prophylaxis using factor VIII preparations for hemophilia A, and (2) etranacogene dezaparvovec

to prophylaxis using factor IX preparations for hemophilia B. ICER's evaluation and intended interpretation assumes a "one size fits all" approach to prophylactic treatment of hemophilia A and B, which may be shortsighted based on the diverse needs and preferences of a heterogeneous patient population.

Several innovative therapeutic options have now been approved, or are currently undergoing investigation, for the prophylactic treatment of patients with hemophilia including extended half-life (EHL) factor VIII and factor IX concentrates, non-replacement therapies, and gene therapies, in addition to existing treatments (e.g., standard half-life [SHL] therapies). Such a wide spectrum of treatments allows for an individualized approach to patient care management, one in which healthcare providers, patients, and caregivers could consider the strengths and weaknesses of all treatment options in order to carefully select an optimal therapeutic pathway for the patient. To this end, an expert panel of the Zurich Hemophilia Forum convened in 2020 to develop an algorithm to facilitate selection of the optimal treatment for hemophilia[8]. Four treatment strategies were considered, including: (1) maintain current treatment, (2) intensify SHL or switch to EHL products with similar frequency, (3) switch to a non-factor replacement product, or (4) switch to EHL products. This algorithm, which considered bleeding phenotype, musculoskeletal status, treatment adherence, venous access, and lifestyle factors, refrained from arbitrarily selecting the newest innovative therapy to market but rather considered patient characteristics and preferences at the center of its determination. Moreover, the World Federation of Hemophilia (WFH) guidelines for the management of hemophilia advocate for tailored prophylaxis regimens based on individualized patient needs[9]. For instance, the guidelines indicate that a patient's behavioral characteristics and lifestyle, among other factors, may directly impact the care she or he receives. Patients who participate in high-impact physical activities may require a higher level of protection than patients who live a more sedentary lifestyle; for those highly active patients, the use of factor replacement therapy may be an appropriate therapeutic option. Therefore, our hope is that ICER's assessment should not lose sight of the individual patient and the interpretation of the evaluation should not risk compromising patients' ability to receive therapies that best fit their clinical history and lifestyle choices.

NN requests for ICER to reconsider aggregated comparators

In ICER's 2020 evaluation of valoctocogene roxaparvovec and emicizumab for hemophilia A without inhibitors, ICER compared the primary interventions to a generalized comparator of all factor VIII treatments[10]. Clinical data for the comparator cohort was based on a single study (SPINART, NCT00623480) of one SHL factor VIII product (Kogenate FS Antihemophilic Factor [Recombinant])[11]. In ICER's current Background and Draft Scope document, it appears that ICER plans to compare valoctocogene roxaparvovec to prophylaxis using factor VIII preparations for hemophilia A (as well as to prophylaxis using emicizumab), and etranacogene dezaparvovec to prophylaxis using factor IX preparations for hemophilia B.

Based on ICER's prior approach to identifying comparator data, it is our assumption that ICER will generalize or aggregate the factor VIII and factor IX comparators in a manner similar to the 2020 evaluation. Doing so in this evaluation will likely present the same limitations and challenges, namely that the prior evaluation did not consider more recently available EHL products. The WFH guidelines recommend keeping factor IX levels in the non-hemophilia range for as long as possible over the dosing interval[9]. While the half-life extension of EHL factor VIII products is approximately 1.5 times that of SHL factor VIII products, the magnitude difference between EHL and SHL factor IX products is far greater, with nearly a 4-fold half-life extension in favor of the EHL therapies[12]. This may have important and deeper implications for ICER's ongoing assessment, especially when considering the impact that reduced dosing frequency may have on potentially improving patient quality of life, treatment adherence, and clinical outcomes associated with the EHL factor IX products[13]. NN therefore requests that ICER consider disaggregating comparators to allow for individual comparison to SHL and EHL therapies.

We appreciate the opportunity to provide input on the scoping document and look forward to engaging with ICER throughout this review.

Sincerely,

Neeraj N. Iyer, PhD
Senior Director & Head, Evidence Synthesis & Value Assessment
Clinical Development, Medical & Regulatory Affairs
Novo Nordisk Inc.

References

1. Esperoct. Package insert. Novo Nordisk/AS; 2019. https://www.novo-pi.com/esperoct.pdf.
2. Novoeight. Package insert. Novo Nordisk/AS; 2020. https://www.novo-pi.com/novoeight.pdf.
3. Rebinyn. Package insert. Novo Nordisk/AS; 2020. https://www.novo-pi.com/rebinyn.pdf.
4. NovoSeven RT. Package insert. Novo Nordisk/AS; 2014. https://www.fda.gov/media/70442/download.
5. Novo Nordisk A/S (2022, Apr 4-). *Safety, Efficacy and Exposure of Subcutaneously Administered NNC0365-3769 (Mim8) Prophylaxis in Children With Haemophilia A With or Without FVIII Inhibitors*. Identifier NCT05306418. https://clinicaltrials.gov/ct2/show/NCT05306418?term=Mim8&phase=2&draw=2&rank=1.
6. Novo Nordisk A/S (2021, Dec 2-). *A Multinational, Open-label, Randomised, Controlled Study to Investigate Efficacy and Safety of NNC0365-3769 (Mim8) in Adults and Adolescents With Haemophilia A With or Without Inhibitors.* Identifier NCT05053139. https://clinicaltrials.gov/ct2/show/NCT05053139?term=Mim8&draw=2&rank=2.
7. Novo Nordisk A/S (2022, March 24-). *Open-label Study Investigating Efficacy, Safety and Pharmacokinetics of Concizumab Prophylaxis in Children Below 12 Years With Haemophilia A or B With or Without Inhibitors.* Identifier NCT05135559. https://clinicaltrials.gov/ct2/show/NCT05135559?term=concizumab&phase=2&draw=2&rank=1.
8. Hermans C., Noone D., Benson G., Dolan G., Eichler H., Jiménez-Yuste V., Königs C., Lobet S., Pollard D., Zupančić-Šalek S., Mancuso ME. Hemophilia treatment in 2021: Choosing the"optimal" treatment using an integrative, patient-oriented approach to shared decision-making between patients and clinicians. Blood Rev. 2022 Mar;52:100890. doi: 10.1016/j.blre.2021.100890. Epub 2021 Sep 29. PMID: 34736780.
9. Srivastava A. , Santagostino E. , Dougall A. , et al. WFH Guidelines for the Management of Hemophilia, 3rd edition . Haemophilia. 2020 : 26(Suppl 6) : 1 - 158 . https://doi.org/10.1111/hae.14046.
10. Institute for Clinical and Economic Review. (2020). Valoctocogene Roxaparvovec and Emicizumab for Hemophilia A without Inhibitors: Final Policy Recommendations.
11. Bayer (2008, March – 2013, November). *Randomized, Controlled, Parallel, Prospective Trial to Evaluate the Effect of Secondary Prophylaxis With rFVIII Therapy in Severe Hemophilia A Adult and/or Adolescent Subjects, as Applicable, Compared to That of Episodic Treatment.* Identifier NCT00623480. https://clinicaltrials.gov/ct2/show/NCT00623480?term=NCT00623480&draw=2&rank=1

12. Ar, M. C., Balkan, C., & Kavaklı, K. (2019). Extended Half-Life Coagulation Factors: A New Era in the Management of Hemophilia Patients. *Turkish journal of haematology :official journal of Turkish Society of Haematology*, *36*(3), 141–154. https://doi.org/10.4274/tjh.galenos.2019.2018.0393.
13. Lambert, T., Benson, G., Dolan, G., Hermans, C., Jiménez-Yuste, V., Ljung, R., Morfini, M., Zupančić-Šalek, S., & Santagostino, E. (2018). Practical aspects of extended half-life products for the treatment of haemophilia. *Therapeutic advances in hematology*, *9*(9), 295–308. https://doi.org/10.1177/2040620718796429.

May 25, 2022

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

Submitted via email: publiccomments@icer.org

RE: Draft Scoping Document for the Assessment of "Gene Therapy for Hemophilia B and Update on Gene Therapy for Hemophilia A"

Dear ICER Review Team,

On behalf of Pfizer Inc., thank you for the opportunity to comment on the draft scoping document for the assessment of "Gene Therapy for Hemophilia B and Update on Gene Therapy for Hemophilia A." We appreciate ICER's efforts to seek input from a broad range of stakeholders. Pfizer is committed to discovering medicines and vaccines that enhance the health of patients, their families, and society, with the goal of offering breakthroughs that will change patients' lives. We are dedicated to working with all stakeholders to ensure access to these breakthroughs and to identify solutions for creating a more effective, efficient, and equitable health care system for patients.

We offer the following feedback on select sections of the draft scoping document for ICER's consideration.

Stakeholder Input

ICER acknowledges that the outcome that matters most to patients is participation, including participation in family life, recreational activities, school activities, and work activities without restriction and that it is impacted not just by the bleeding events but by "fear of bleeding events". ICER may wish to consider "fear of bleeding events" in the cost-effectiveness model using subdomains of the Haem-A-QoL (ie, sport/leisure; work/school domains). The omission of this from an ICER analysis could have important implications to stakeholder understanding of the clinical and economic value of the therapies under consideration.

The ICER framework includes both quantitative and qualitative comparisons to ensure the full range of benefits and harms are assessed, including those not typically captured in the clinical evidence, such as patient experience. For example, ICER may wish to consider incorporating data from patient preference studies recently published. [1-4]

Scope of Clinical Evidence Review

In the "Outcomes" section, ICER highlights that it plans to focus on "Patient Important Outcomes" and six core outcomes considered by coreHEM crucial for evaluating the effectiveness of gene therapy: frequency of bleeds, factor activity level, duration of expression, chronic pain, mental

health status and utilization of healthcare system (direct costs). We make the following recommendations:

- We recommend that ICER clarify its definition of "Burden of Therapy" and consider include storage and inventory handling as suggested by Tischer et al.[4]
- As it relates to duration of expression, the ICER scoping document acknowledges that different assays can give markedly different responses. Recent data suggests this discrepancy is amplified at low factor levels.[5] We suggest ICER to make it clear how this will be taken into account when assessing durability of treatment effect and treatment failure.
- We recommend that ICER clarify its definition of "immune response to gene therapy" (i.e., will this be based on elevated ALT, use of immunosuppression, or both?) and how will duration of immunosuppression be considered.

ICER mention that over higher ranges the factor level is an excellent surrogate and that a therapy that provides normal, sustained factor levels would be expected to achieve normal hemostasis in patients with hemophilia. ICER may wish consider that factor levels in the moderate range (≤5%) – either as constant levels with gene therapy, or as exogenous factor trough – may provide satisfactory hemostasis as it relates to spontaneous joint bleeding, but may not provide adequate hemostasis in cases of intense activity, trauma and/or surgery.

Population

ICER mention that the population of focus will be adults ≥ 18 years of age with hemophilia A or B without inhibitors who would be appropriate for routine prophylaxis with factor replacement. We suggest ICER to clarify severity of the disease in consideration.

Scope of Comparative Value Analyses

We support ICER's proposal to compare each treatment in the review to prophylaxis with factor preparations (and emicizumab for Valoctocogene roxaparvovec) and will compare etranacogene dezaparvovec to prophylaxis using factor IX preparations. We recommend ICER to clarify whether standard half-life and/or extended half-life factors will be considered in the cost effectiveness model.

We support ICER's proposal to update ICER's prior simulation model to assess, separately, the cost-effectiveness of etranacogene dezaparvovec relative to prophylaxis using factor IX for hemophilia B. We also support that the model structure for hemophilia B to be closely resembling the prior model for hemophilia A.

We recommend that ICER revisit using utilities tied to Pettersson score (Cumulative Joint Damage) as it is not currently used in clinical practice and may not capture Quality of Life impairment due to lifestyle restrictions. The Pettersson score-based utility adjustment changes very little (if at all) over patients' lifetime. We suggest ICER to clarify how disability and functional limitations prior to arthropathy that leads to replacement surgery will be considered in the economic evaluation as well as disability paradox and treatment burden.

We also recommend ICER clarify its definition of "treated bleeds not into a target joint" health state and how the model treat "target joint" differently from a non-target joint. And, lastly, ICER should consider adherence to factor in the cost effectiveness model. It has been reported that adherence to prophylaxis is suboptimal[6] and that suboptimal adherence impacts outcomes.[7,8] Gene therapy effectively removes suboptimal adherence from the variables impacting outcomes in the real-world, and should be considered.

We hope that these comments are useful to ICER and look forward to further discussions throughout the review process.

Sincerely,

Gergana Zlateva, PhD
Vice President, Patient & Health Impact, Oncology
Pfizer Inc, 235 East 42 Street, New York, NY 10017

References

1. Woollacott I, Morgan G, Chowdary P, et al. Examining patient and professional perspectives in the UK for gene therapy in haemophilia. *Haemophilia*. Apr 19 2022;doi:10.1111/hae.14572
2. Witkop M, Morgan G, O'Hara J, et al. Patient preferences and priorities for haemophilia gene therapy in the US: A discrete choice experiment. *Haemophilia*. Sep 2021;27(5):769-782. doi:10.1111/hae.14383
3. van Overbeeke E, Hauber B, Michelsen S, et al. Patient preferences for gene therapy in haemophilia: Results from the PAVING threshold technique survey. *Haemophilia*. Nov 2021;27(6):957-966. doi:10.1111/hae.14401
4. Tischer B, Marino R, Napolitano M. Patient preferences in the treatment of hemophilia A: impact of storage conditions on product choice. *Patient Prefer Adherence*. 2018;12:431-441. doi:10.2147/ppa.S151812
5. Pittman D, Carrieri C, Soaeas H, et al. Preliminary field study results suggest differences in FIX activity based on assay from gene therapy trial patients expressing R338L high-activity variant of FIX. *Haemophilia*. 2022;28(S3):45-46. doi:DOI: 10.1111/hae.14537
6. Armstrong EP, Malone DC, Krishnan S, Wessler MJ. Adherence to clotting factors among persons with hemophilia A or B. *Hematology*. Apr 2015;20(3):148-53. doi:10.1179/1607845414y.0000000176
7. O'Hara J, Noone D, Jain M, et al. Clinical attributes and treatment characteristics are associated with work productivity and activity impairment in people with severe haemophilia A. *Haemophilia*. Nov 2021;27(6):938-946. doi:10.1111/hae.14302
8. Bago M, Butkovic A, Preloznik Zupan I, et al. Association between reported medication adherence and health-related quality of life in adult patients with haemophilia. *Int J Clin Pharm*. Dec 2021;43(6):1500-1507. doi:10.1007/s11096-021-01270-x

May 25, 2022

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

Re: ICER's Review of valoctocogene roxaparvovec for hemophilia A and etranacogene dezaparvovec for hemophilia B

To Whom It May Concern:

The National Hemophilia Foundation (NHF), Hemophilia Federation of America (HFA), and the Coalition for Hemophilia B are national non-profit organizations that represent individuals with bleeding disorders across the United States. Our missions are to ensure that people with hemophilia (PwH) and other inherited bleeding disorders have timely access to quality medical care, therapies, and services, regardless of financial circumstances or place of residence. All three organizations accomplish this through advocacy, education, and research. Thank you for the opportunity to provide comment on the Draft Scoping Document for valoctocogene roxaparvovec for hemophilia A and etranacogene dezaparvovec for hemophilia B.

Hemophilia and Gene Therapy

NHF and HFA have participated in two prior ICER hemophilia reviews, with CHB now joining for this new review. With limited space allowed for this letter, we encourage ICER to review all our prior comments. Although ICER has familiarity with hemophilia A, there are important differences between hemophilia A and hemophilia B and the existing and pipeline treatment options available to each. While both populations share a hope for improved treatment and quality of life (QoL), the clinical trial results reported to date suggest that PwHB are closer to a treatment that may relieve them from the need for ongoing prophylaxis than PwHA. There are marked differences between the populations with respect to eligibility for treatment, durability of therapy, the potential for post-administration bleeding, and adverse events following vector administration. These differences are notable given the irreversible once in a lifetime opportunity of AAV gene therapy.

Cost-sharing, step-therapy, and other restrictive insurance mechanisms should be considered within the overall review. The "financial toxicity" associated with high-cost hemophilia treatments remains an on-going concern to fair and equitable access. We look forward to working with ICER to further delineate these concerns in the policy roundtable associated with this review and the "*Cornerstones of 'Fair' Drug Coverage: Appropriate Cost-Sharing and Utilization Management Policies for Pharmaceuticals"* updates.

General Comments

When ICER last reviewed hemophilia, it noted several areas for which there was no evidence. The global hemophilia community has worked diligently to address these gaps.

In particular, we wish to call ICER's attention to the recently published Haemophilia supplement, *Is the World Ready for Gene Therapy?* [REF *Haemophilia* Supp] This includes a literature review of published clinical research data applied to the hemophilia value framework [REF O'Mahony 2018], as well as an article assessing outcomes for extended half-life (EHL) replacement factor therapy, non-factor replacement therapies, and gene therapy (GT) compared to standard half-life replacement factor therapy. [REF Skinner 2022]

We have previously urged ICER to recognize the full set of patient-important outcomes, even where data are lacking. Now that new data are available, we ask that ICER integrate the new outcomes data into the model with

appropriate weight and recognition, rather than just discuss them in the narrative. Such recognition is important to fully inform the current value assessment.

Background

While we understand why so much of the discussion focuses on people with severe hemophilia, we note that people with hemophilia of all severity levels must modify their lifestyles to reduce the risk of serious bleeding. We call ICER's attention to a recent publication wherein matched data for PwH to control populations without a bleeding disorder demonstrate a significant health disutility even with milder states of hemophilia. [REF Chai-Adisaksopha 2020] Principles of health equity would dictate that all PwH should be able to attain their full potential for health and well-being, not just those with severe hemophilia. [REF WHO]

Stakeholder Input

We agree with ICER's note about the importance of surveillance of gene therapy recipients post vector infusion. This is why a global multi-stakeholder group has established the World Federation of Hemophilia (WFH) Gene Therapy Registry, to which the American Thrombosis and Hemostasis Network (ATHN) will contribute data for Americans who undergo gene therapy. [REF Konkle 2020]

Selecting the Appropriate Value Framework

NHF and HFA support ICER's decision to use 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 these reviews. Both treatments clearly fit within the ultra-rare/SST criteria: they would be used in a patient population smaller than 10,000 people. There is little chance of future expansion that would extend the size of the treated population above 20,000 individuals. The treatments may offer a major gain in improved quality of life and/or length of life, and both are high-impact SSTs. [REF Goodman 2022]

Populations

When considering populations for gene therapy, please note that PwH with a prior history of factor VIII / IX inhibitors and children are only some of the exclusions. For PwHA and PwHB, those with a pre-existing immunity to the vector of interest (with the possible exception of one hemophilia B vector) or who are HIV+ may (depending on the vector) also be excluded. People with chronic liver disease and women are two other notable exclusions.

Comparators

Given the advanced stage of efanesoctocog alfa for the treatment of hemophilia A, we recommend it be added as a comparator of interest for this review for PwHA. The pivotal phase 3 trial is complete and top-line results have been reported. [REF SOBI / Sanofi press release]

There are unique differences in hemophilia A and B standard of care. Unlike hemophilia A, we do not believe it is possible to blend the hemophilia B EHL into one category. They should be compared individually given notable differences between them (e.g., >60% of FIX in the extravascular space so there is no real correlation between trough levels and ABR. The volume of distribution is different for each EHL FIX). [REF Hermans WFH 2022]

Finally, as noted above, there are substantial new data available for comparators of interest. Thus, we believe ICER's prior analysis for emicizumab for PwH without inhibitors should be updated and included within this review to ensure an appropriate comparison with valoctocogene roxaparvovec.

Outcomes

Thank you for recognizing and incorporating the coreHEM core outcome set. [REF Iorio 2018] Of note, a content validated patient-reported outcome measure (PROM) for the mental health outcome has recently been developed and will fill the remaining gap in tools to measure core outcomes. [REF Clearfield 2022]

We ask that you add steroid use as an outcome of interest, given the reported required use of glucocorticoids in the two-year data analysis for valoctocogene roxaparvovec (79.1% of participants received steroids for a median treatment duration of 230 days), and the high proportion of related adverse events. [REF Ozelo 2022]

We recommend that ICER characterize burden of therapy for both interventions and comparators. Gene therapy clinical trial participants have indicated that the post-vector monitoring burden is significant, requiring frequent lab tests and life changes (e.g., barrier contraception and abstention from alcohol). These factors could influence QoL calculations and/or patient compliance outside of the highly controlled environment of a clinical trial.

We encourage ICER to use both generic and hemophilia-specific PROMS when assessing health-related QoL. Recent studies indicate the presence of a "disability paradox" among PwH, who reported higher health states than the general population, suggesting the impact of hemophilia may be underestimated if general population value sets are used. [REF O'Hara 2021]

Today, factor activity level remains the driver of clinical decision making. Linking factor activity level to clinical outcomes is important for this and future evaluations of novel therapies. Although some have noted low bleeding rates even as factor activity levels taper post vector infusion, we are not aware of any published evidence to correlate this finding to patient important outcomes or long-term joint health. [REF Ozelo 2022] We continue to believe achieved factor activity level (e.g., the restoration of lacking clotting capacity) is the best indicator of anticipated long-term clinical outcome and discourage anything besides the most realistic assumptions about durability. [REF Kaczmarek 2021, Pierce 2020]

A model based primarily on joint outcomes (e.g., the Hemophilia Joint Health Score (HJHS)) fails to capture the potential transformative and health related QoL changes that are increasingly evident with newer therapies. We also ask ICER to clarify how it will compare joint bleeding, target joints, and problem joints as the definitions or method for calculation used within clinical studies vary.

Societal costs are also an important input. Costs associated with lost time from work for patients and caregivers are significant and have been estimated based on a burden of illness analysis. [REF Zhou 2015]

The ability to withstand minor trauma without the need for factor replacement is an important feature of many recent therapeutic advances including gene therapy if adequate factor expression is achieved.

In addition to updating the list of outcomes of interest, we also suggest ICER review the coreHEM core outcome set for an updated list of adverse events of interest within gene therapy. These are grouped in 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. Recent events with AAV therapy including thromboses, requirement for prophylactic anticoagulant treatment, as well as three reports of cancer (deemed unrelated to the vector) highlight the many unknowns. [REF Pierce 2018]

The importance of maintaining higher trough levels is becoming evident with EHL FIX and non-replacement therapies. The level of adherence can also impact the outcome of long-term joint health. New therapies increase the therapeutic protection window and allow spontaneity in a patient's life. Gene therapy removes these issues and could be reported in terms of a lifetime area under the curve (AUC) above 3-4 defined levels. This could be calculated in the model and clearly show the comparison of lifetime AUC across all products

An important variable in the decision-making process is the fact that AAV gene therapy can be administered only a single time. The immune response will preclude re-administration of any other currently identified AAV vectors.

At present, no solution exists for this problem, meaning that if a patient gets a suboptimal response or loses activity over a comparatively short period, they have lost their opportunity for subsequent AAV gene therapy. [REF Kaczmarek 2021] Given the rapid advances made in the field, and the expectation that the added risk of the unknowns of gene therapy should translate into a "once and done" therapy, this is a more critical variable in the decision-making process for PwHA compared to PwHB.

Scope of Comparative Value Analysis

The ICER review and budget impact analysis should be grounded in a realistic expectation of the uptake of gene therapy by PwH. With particular reference to valoctocogene roxaparvovec, until questions related to durability, reliability and expected factor activity level are better understood, we do not anticipate a rapid uptake of hemophilia A gene therapy. The uptake of etranacogene dezaparvovec by the hemophilia B population will likely vary. Many PwH will also be concerned about post-gene therapy access to prophylaxis or replacement therapy for breakthrough bleeding events or if the vector efficacy tapers. Real-world experience will be critical to inform an evidence-based return to prophylaxis ratio and how payers have responded.

Lastly, we wish ICER to take note of a recent publication summarizing key considerations in health technology assessment (HTA) for hemophilia. [REF O'Hara and Neuman 2022] The major value drivers in a model, in addition to drug pricing itself, will be based on assumptions about duration of effect and savings/cost offsets from reduced use of replacement therapy. Given the uncertainties around the long-term gene therapy use, clinical trial data should be extrapolated ~10 years, using scenarios that consider different durations of effect. We encourage ICER to consider the difficulties in conducting randomized controlled trials for gene therapy and to consider intra-patient data as evidence of comparative effectiveness. Assessment methodologies and modelling configurations need to evolve to fully capture the value of gene therapy, including patient meaningful outcomes, in a validated and quantitative fashion.

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 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 PwH who will adopt these potentially transformative novel therapies at their earliest opportunity - and other PwH 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,

Leonard A. Valentino, M.D.
Chief Executive Officer
National Hemophilia Foundation

Sharon Meyers, EdD, CFRE
President & CEO
Hemophilia Federation of America

Kim Phelan
Chief Operating Officer
Coalition for Hemophilia B

REFERENCES

Chai-Adisaksopha C, Noone D, Curtis R, Frick N, Nichol M, Germini F, O'Mahony B, Page D, Stonebraker J, Skinner M, Iorio A. Non-severe haemophilia: Is it benign? – Insights from the PROBE study. Haemophilia. 2020;00:1–8. https://doi.org/10.1111/hae.14105

Clearfield, E. ISPOR 2022. PCR45 - Development of a Patient-reported Outcome Measure (PROM) to Fully Report a Proposed Core Outcome Set.

Goodman, C, Berntorp, E, Wong, O. Alternative Payment Models for Durable and Potentially Curative Therapies: the Case of Gene Therapy for Haemophilia A. Haemophilia. 2022; 28(Suppl. 2): 27– 34. https://doi.org/10.1111/hae.14425

Haemophilia. Is the World Ready for Gene Therapy? (2022), Haemophilia, 28: 1-41. https://doi.org/10.1111/hae.14538

Hermans, C. Variations in efficacy and extravascular distribution of FIX. WFH Congress 2022, Coagulation Product Safety, Supply, and Access workshop. 8 May 2022.

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. https://doi.org/10.1111/hae.13504

Kaczmarek et al., Eliminating Panglossian thinking in development of AAV therapeutics, Molecular Therapy (2021), https://doi.org/10.1016/j.ymthe.2021.10.025

Konkle BA, Pierce GF, Coffin D, Naccache M, Clark C, George LA, Iorio A, O'Mahony B, Pipe S, Skinner MW, Watson C, Peyvandi F, Mahlangu JN, for the ISTH subcommittee on Factor VIII, Factor IX and rare bleeding disorders. Core data set on safety, efficacy and durability of hemophilia gene therapy for a global registry: communication from the SSC of the ISTH. J Thromb Haemost. 2020 Oct. https://doi.org/10.1111/jth.15023

O'Hara, J, Neumann, PJ. Health technology assessment for gene therapies in haemophilia. Haemophilia. 2022; 28(Suppl. 2): 19– 26. https://doi.org/10.1111/hae.14413

O'Hara, J., Martin, A.P., Nugent, D., Witkop, M., Buckner, T.W., Skinner, M.W., O'Mahony, B., Mulhern, B., Morgan, G., Li, N. and Sawyer, E.K. (2021), Evidence of a disability paradox in patient-reported outcomes in haemophilia. Haemophilia, 27: 245-252. https://doi.org/10.1111/hae.14278

O'Mahony, B, Dolan, G, Nugent, D, Goodman, C, on behalf of the International Haemophilia Access Strategy Council. Patient-centered value framework for haemophilia. Haemophilia. 2018; 24: 873– 879. https://doi.org/10.1111/hae.13456

Ozelo, M.C., Mahlangu, J., Pasi, K.J., Giermasz, A., Leavitt, A.D., Laffan, M., Symington, E., Quon, D.V., Wang, J.-D., Peerlinck, K., Pipe, S.W., Madan, B., Key, N.S., Pierce, G.F., O'Mahony, B., Kaczmarek, R., Henshaw, J., Lawal, A., Jayaram, K., Huang, M., Yang, X., Wong, W.Y., Kim, B., 2022. Valoctocogene Roxaparvovec Gene Therapy for Hemophilia A. New England Journal of Medicine 386, 1013–1025. doi:10.1056/nejmoa2113708

Pierce, G.F., Kaczmarek, R., Noone, D., O'Mahony, B., Page, D., and Skinner, M.W. (2020), Gene therapy to cure haemophilia: Is robust scientific inquiry the missing factor? Haemophilia. doi:10.1111/hae.14131
Pierce, GF, Iorio, A. Past, present and future of haemophilia gene therapy: From vectors and transgenes to known and unknown outcomes. Haemophilia. 2018; 24(Suppl. 6): 60- 67. https://doi.org/10.1111/hae.13489

Skinner, MW, Dolan, G, Eichler, H, O'Mahony, B. A preliminary application of a haemophilia value framework to emerging therapies in haemophilia. Haemophilia. 2022; 28(Suppl. 2): 9– 18. https://doi.org/10.1111/hae.14511

Sobi / Sanofi. Efanesoctocog alfa met primary and key secondary endpoints in pivotal study in hemophilia A, demonstrating superiority to prior factor prophylaxis treatment – Sanofi. https://www.sanofi.com/en/media-room/press-releases/2022/2022-03-09-07-00-00-2399557. Last Accessed 21 May 2022.

World Health Organization https://www.who.int/health-topics/health-equity. Last accessed 20 May 2022

Zhou ZY, Koerper MA, Johnson KA, et al. Burden of illness: direct and indirect costs among persons with hemophilia A in the United States. Journal of medical economics. 2015;18(6):457-465.