

October 10, 2022

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

Re: Comments on “Gene Therapy for Hemophilia B and Update on Gene Therapy for Hemophilia A: Draft Evidence Report”

ICER Hemophilia Review Team,

On behalf of BioMarin, I appreciate the opportunity to provide written comments on the Institute for Clinical and Economic Review (ICER)’s Draft Evidence Report for the ongoing assessment of valoctocogene roxaparvovec, BioMarin’s investigational gene therapy for hemophilia A.

BioMarin appreciates ICER’s recognition of the long-term value of valoctocogene roxaparvovec in saving costs and improving health compared to emicizumab prophylaxis. BioMarin is in general agreement with the economic model structure and assumptions and appreciates that ICER incorporated the potential impact of an innovative payment model, which BioMarin plans to offer at the time of product launch, in the base-case economic model.

We would like to provide the following comments on the Draft Evidence Report for ICER’s consideration.

BioMarin believes that ICER’s economic model may underestimate the health benefit achievable with valoctocogene roxaparvovec as measured by quality-adjusted life-years (QALY), due to:

- 1. Use of non-comparable bleeding data for the emicizumab arm.** As acknowledged by ICER in the Draft Evidence Report, the most relevant comparator population for valoctocogene roxaparvovec is Group D of the HAVEN 3 clinical trial of emicizumab, as those study participants had been receiving adequate factor VIII (FVIII) prophylaxis prior to study treatment. However, in the Economic Model section of the report, the input for the annualized bleeding rate (ABR) for the emicizumab arm appears to be based on Group B, derived from *“Participants receiving previous episodic therapy with factor VIII”*.¹ In Group D, the ABR for all bleeds was 3.3², compared with 2.6 for Group B¹ as currently used in ICER’s economic model. BioMarin recommends that ICER updates the values for emicizumab ABR with HAVEN 3 Group D data to reflect a population most comparable to the study populations of valoctocogene roxaparvovec.
- 2. Over-estimation of bleeds in the valoctocogene roxaparvovec arm.** The presumed high ABR at FVIII activity level <5 IU/dL used in the model, based on epidemiological data of mild and moderate hemophilia, and the simplified assumption related to return to prophylaxis lead to over-estimation of bleeds for the valoctocogene roxaparvovec arm. A more reasonable

assumption to inform the relationship between bleeds and exposure to transgene-produced factor activity level should be informed by valoctocogene roxaparvovec clinical trial data. Recent ad-hoc analysis from GENEr8-1 (NCT03370913) suggested that valoctocogene roxaparvovec-treated patients with FVIII activity level <5 IU/dL who did not switch back to prophylaxis had a median ABR of 3.07 (all bleeds)³ rather than >7 as currently estimated in the model. Patients who switched to prophylaxis had a median ABR of 6.89 (all bleeds), which is consistent with epidemiological data.⁴ The median FVIII activity level at switching was 1.95 IU/dL (by one-stage assay).³ Based on the above evidence, BioMarin advises ICER to cap ABR (all bleeds) at 3.07 for the remaining cohort rather than an ABR (all bleeds) of ~ 7 projected from epidemiological data.

- Potential under-estimation of health-state utility benefit associated with valoctocogene roxaparvovec.** BioMarin appreciates that ICER has listened to the community voice and considered the broad evidence base by implementing an annual utility increment in the valoctocogene roxaparvovec arm for patients who remain off prophylaxis. We would like to note however that 0.01 utility difference in the base-case model is likely to be a lower-bound estimate of the true utility benefit. The incremental utility difference of 0.01 was determined for treatment administration alone (one-time administration with 10-year benefit vs. 1-2 subcutaneous injections per month) from a patient preference/time trade-off study.⁵ Additional benefits of a gene therapy, including the freedom to pursue sports, and having a more active lifestyle and career choices, have been demonstrated in a range of patient-reported outcomes from GENEr8-1 and are likely to translate into additional utility gain.⁵ The same patient preference/time trade-off study also showed that improvements in other coreHEM measures, such as change in mental health and chronic pain, also have a significant impact on patient treatment preference and health state utilities.⁵ Nevertheless, health-state utility difference between gene therapy and routine prophylaxis, including emicizumab, warrants more research due to multiple well-recognized issues, such as the sensitivity of the generic utility tools, and the disability paradox in hemophilia. BioMarin is committed to continue working with the patient community and experts to generate further evidence on this topic. Overall, BioMarin agrees with the use of 0.01 as a conservative estimate for the utility difference.

BioMarin is concerned that the given clinical rating (C++) for the net health benefit of valoctocogene roxaparvovec vs. FVIII prophylaxis does not reflect the totality of evidence to date. Based on clinical efficacy and safety results already available from the largest phase 3 program and longest follow up (from the phase 1/2 study) of any gene therapy to date, BioMarin believes that the evidence supports a rating of B+.

- Efficacy:** The net health benefit of valoctocogene roxaparvovec vs. FVIII prophylaxis has been demonstrated in the largest phase 3 trial (GENEr8-1; NCT03370913) and the longest follow up (from the phase 1/2 trial; NCT02576795) of any investigational gene therapy. In GENEr8-1 (N=134), 112 participants underwent a prospective observation period of at least 6 months prior to valoctocogene roxaparvovec administration to establish baseline ABR and FVIII use while receiving standard-of-care FVIII prophylaxis. After 2 years of follow up post valoctocogene roxaparvovec administration, there was a 77% reduction in mean total ABR and an 85% reduction in mean treated ABR over the whole study period compared with baseline levels associated with FVIII prophylaxis.^{6,7} The relative benefit of valoctocogene roxaparvovec on ABR vs. baseline FVIII prophylaxis was clinically and statistically significant

($P < 0.001$) and was consistent between year 1 and year 2.⁶ In addition to ABR reduction, valoctocogene roxaparvovec was associated with a 98% reduction in use of FVIII compared with baseline over 2 years of follow up ($P < 0.001$).⁶ Notably, participants in GENEr8-1 demonstrated broad and consistent improvements in health-related quality of life sustained through 2 years post gene transfer.⁸ 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*.⁸ 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.⁸ The observed benefits associated with valoctocogene roxaparvovec vs. FVIII prophylaxis in bleeding control, FVIII use, and quality of life warrant an incremental improvement rating.⁹

Although post-administration FVIII activity exhibited a steady decline over time, the rate of decline became shallower after the initial decline, proportionate to the initial peak.¹⁰ Importantly, ICER, in the Clinical Benefit section of the report, appear to have misinterpreted valoctocogene roxaparvovec *1-year data from GENEr8-1* to assume that the majority of trial participants resumed prophylaxis once their FVIII activity levels were < 5 IU/dL (page 10). On the contrary, existing data suggest a sustained treatment effect, with only 6 ($< 5\%$) participants from GENEr8-1 returning to prophylaxis ($N = 134$) within 2–3 years of follow up, and all participants from the phase 1/2 study 6E13 vg/kg cohort remaining off prophylaxis through 6 years.^{6,9}

The hemostatic efficacy and quality-of-life benefit of valoctocogene roxaparvovec for patients with persistent low endogenous FVIII levels warrants further research. However, we believe it is premature for ICER to conclude that the benefit of valoctocogene roxaparvovec is ‘short-lived’. Given the importance of ABR, FVIII use, and patient’s quality of life as patient-relevant outcome measures when determining treatment effectiveness for hemophilia A, we believe there is high confidence in the evidence base to date to demonstrate incremental net health benefit for valoctocogene roxaparvovec vs. FVIII prophylaxis as a one-time infusion for people with severe hemophilia A who want the opportunity to live bleed-free for years without prophylaxis.

2. **Safety:** In the report, ICER notes that a high risk of elevated liver enzymes requiring prolonged corticosteroid therapy is a concern with valoctocogene roxaparvovec. Most adverse events from GENEr8-1 trial were of grade 1 or 2, and the frequency of adverse events decreased over time.^{6,11} No participants withdrew from the study because of adverse events and none showed development of FVIII inhibitors. No thrombotic events, drug-related cancers, or drug-related deaths have been reported. It is important to note that the GENEr8-1 protocol was flexible with regard to oral corticosteroid treatment post infusion, which was initiated at the investigator’s discretion based on elevations in alanine aminotransferase (ALT) above the upper limit of the normal range or falls in FVIII activity post-valoctocogene roxaparvovec infusion. It is acknowledged that investigator conduct in the trial demonstrated a propensity for steroid use.¹¹ The European label of valoctocogene roxaparvovec reflects a more restrained use of steroids.¹² In the absence of an alternative cause for the ALT elevation, a corticosteroid regimen should be promptly initiated at a daily dose of 60 mg prednisone (or equivalent dose of another

corticosteroid) for 2 weeks. The daily corticosteroid dose can be gradually tapered in a stepwise manner over 6 weeks. We will monitor the use of immunosuppressant regimens in the real world in Europe, and it is expected that immunosuppression with steroids will be less intensive than was observed in the clinical trials.

3. **Suboptimal adherence with prophylaxis regimens compromises outcomes in the real world.** One-time administration with gene therapy eliminates major issues with adherence to routine prophylaxis. BioMarin recommends that ICER’s comparative effectiveness review takes real-world outcomes into consideration: adherence with FVIII prophylaxis has been reported to vary widely, with some patients self-reporting adherence to be in the range of 30–96%.¹³ Missed doses have consequences. In the 270-902 study (a non-interventional lead-in study of GENEr8-1), adherence to FVIII prophylaxis in both pre-baseline and on-study period was >90%.¹⁴ Despite high levels of adherence to prophylaxis, participants had continued occurrence of spontaneous and joint bleeding events requiring treatment and leading to impaired physical functioning. It is of note that valoctocogene roxaparvovec has demonstrated clinical superiority over baseline FVIII prophylaxis in the highly adherent cohort from the 270-902 study.¹⁵ Adherence in the real world is expected to be much lower than in the 270-902 study, therefore, one might expect a larger magnitude of benefit if compared with a cohort of patients with more usual, variable levels of adherence to prophylaxis. We believe this is a distinction that merits consideration when defining the clinical benefit rating for valoctocogene roxaparvovec vs. standard-of-care treatments.

The outcomes-based warranty agreement that BioMarin plans to offer for valoctocogene roxaparvovec is designed to address variability and durability concerns for payers and health systems. BioMarin agrees with ICER that this outcomes-based warranty design should be incorporated and remain in the base case modelling.

Finally, BioMarin would like to make a few factual corrections in the Draft Evidence Report.

Misinterpretation of valoctocogene roxaparvovec 1-year data

On page 10 of the Draft Evidence Report, it is stated “*In the GENEr8-1 trial, 16 participants (12.1%) had factor VIII levels < 5 IU/dL and 12 participants (9.1%) had levels < 3 IU/dL. Presumably, the majority of these continued factor prophylaxis, though the details are not reported*”. It is not accurate to assume that the majority of trial participants with low factor level (<5 IU/dL) continued factor prophylaxis. On the contrary, in the 2-year GENEr8-1 results presented at EAHAD 2022¹⁶ and BioMarin’s previous data submission to ICER, BioMarin reported that only 5 of 31 participants with factor <5 IU/dL (by chromogenic substrate assay) at week 104 had switched to prophylaxis (1 participant switched to prophylaxis at factor >5 IU/dL). The majority continued to be prophylaxis-free and many did not experience bleeding to date.

Inaccurate reference to valoctocogene roxaparvovec clinical rating in ICER 2020 review

On page ES2, it is stated that ICER gave valoctocogene roxaparvovec a C++ rating compared with factor VIII prophylaxis in its 2020 review (page ES2). This statement is inaccurate. ICER rated the evidence as “*promising but inconclusive*” (P/I) in the 2020 review.¹⁷

Inconsistency in the reference to utility increment used in Hemophilia A model

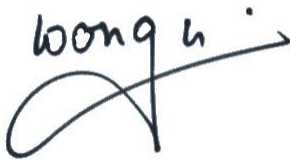
In the Draft Evidence Report, ICER makes three different references to the utility gain implemented in the Hemophilia A model:

- “*Valoctocogene roxaparvovec was associated with a utility gain of 0.01 based on data submitted to ICER*” ([page 18](#))
- “*Valoctocogene roxaparvovec was associated with a fixed utility gain of 0.02 per cycle as long as patients did not switch therapies based on data submitted by BioMarin*” ([page E4](#))
- “*..fixed utility gain of 0.03 was used for both gene therapies in their respective models based on EQ5D data provided by BioMarin and CSL Behring*” ([page E12](#))

Based on the model results, we believe that ICER referenced the patient preference/time trade-off research and implemented a utility gain of 0.01 per year in the model. Please update these references to ensure consistency in the Updated Evidence Report.

I appreciate the opportunity to provide feedback to the ICER’s Draft Evidence Report. We look forward to continuing to work with ICER to refine the evidence report as related to valoctocogene roxaparvovec. Please contact me with questions or clarifications.

Sincerely,

A handwritten signature in black ink, appearing to read "Wong Y", with a stylized flourish extending from the end.

Wing Yen Wong, MD
Special Advisor to President of Worldwide Research & Development
BioMarin Pharmaceutical, Inc.

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October 11, 2022

Steven D. Pearson, MD, MSc
President
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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: Effectiveness and Value Draft Evidence Report” dated September 13, 2022

Dear Dr. Pearson:

On behalf of CSL Behring, we welcome the opportunity to give feedback on the Institute for Clinical and Economic Review (ICER)’s Draft Evidence Report for the assessment of “Etranacogene Dezaparvovec for Hemophilia B”.¹ This review is timely given the US Food & Drug Administration (FDA)’s decision on May 24, 2022 to accept etranacogene dezaparvovec biologics license application for priority review.² CSL Behring appreciates that ICER has conducted this work and has welcomed all of the mutual feedback and advice throughout this process. Etranacogene dezaparvovec may be available to patients soon. This assessment provides valuable insight into the clinical and economic benefits of this therapy for people living with hemophilia B (PWHB). We agree with ICER that etranacogene dezaparvovec will provide a more cost-effective one-time therapy than routine prophylaxis of Factor IX (FIX) therapies.

First, we would like to commend ICER’s use of the best available data to model the comparative efficacy of etranacogene dezaparvovec. We agree with ICER’s approach of modeling both arms of this analysis using data from HOPE-B rather than doing a naïve or indirect treatment comparison between HOPE-B and FIX prophylaxis clinical trials. This approach allows for the most accurate estimate of the relative effectiveness between etranacogene dezaparvovec and FIX prophylaxis given the currently available data. We also appreciate the difficulty in extrapolating FIX activity beyond trial follow-up and we agree with the use of Phase 2B trial data with more follow-up than HOPE-B to extrapolate FIX activity.^{1; 3} We find the use of both high and low FIX activity levels per year projections in sensitivity analyses to provide a robust estimate of uncertainty. Overall, we commend ICER on a well-conducted review with numerous scenario and sensitivity analyses. We believe this analysis properly contextualizes the benefits of etranacogene dezaparvovec and other gene therapies for PWHB.

Beyond those points, we do have some recommendations for further consideration after reviewing the report closely. Suggestions are below, separated by the section of the report in which the recommendation was found.

Section 3.2 Comparative Clinical Effectiveness: Uncertainties and Controversies

Under the uncertainties and controversies section, ICER notes that “*it is not yet clear etranacogene dezaparvovec will have the same long-term decline in factor levels that has been observed with*

valoctocogene roxaparvovec, though the decline appears to be less rapid, if it occurs at all”. CSL Behring appreciates that extrapolating factor activity beyond the follow-up period of a trial is innately uncertain. However, we disagree with this phrasing.

First, we note that, mechanistically, there is a significant scientific rationale to anticipate that transgene expression of FIX will be more sustained than transgene expression of Factor VIII (FVIII). For example, both etranacogene dezaparvovec and valoctocogene roxaparvovec target hepatocytes to produce FIX and FVIII, respectively.³⁻⁵ However, native production of FIX occurs exclusively within the hepatocytes, while FVIII is produced within sinusoidal endothelial cells of the liver.⁶ Thus, etranacogene dezaparvovec more closely approximates endogenous production of its clotting factor than valoctocogene roxaparvovec by targeting cells that naturally produce its transgene product. Furthermore, the comparative size of the FVIII gene in contrast to the FIX gene requires the use of shorter promoter elements to fit within the AAV5 cassette size, which necessitates higher vector doses to achieve similar response.⁶ Higher vector doses are associated with loss of transgene expression due to elevation of liver aminotransferases.⁷ Recently, Herzog and Pierce (2022) concluded that, while there are uncertainties around the comparativeness of vector doses/titers and infectivity, the most obvious hypothesis at first glance to explain the greater variability in durability in Hemophilia A gene therapy trials in contrast to Hemophilia B gene therapy trials is related to FVIII itself.⁶ We encourage ICER to add statements that contextualize the differences observed in durability between etranacogene dezaparvovec and valoctocogene roxaparvovec.

In addition to the comments above, there is a more obvious objection. Published data from 3 years of the phase 2 study of etranacogene dezaparvovec and five years of a study of the AMT-060 precursor (which differs only in using wild-type rather than Padua FIX) clearly demonstrate lower levels of decline than trials of valoctocogene roxaparvovec.^{3; 5; 8} While we acknowledge that we cannot say for certain that etranacogene dezaparvovec will have *no* long-term decline of FIX production, any decline seen within the first three to five years will be more gradual than in valoctocogene roxaparvovec. While the second clause of the ICER quote does implicitly acknowledge this, we note that the phrase “*the same long-term decline*” indicates that is possible that etranacogene dezaparvovec and valoctocogene roxaparvovec could have similar patterns of gene expression decline. However, patterns of decline will differ in at least the first three years based on the best available data. Therefore, we suggest to rephrase this to “*it is not yet clear etranacogene dezaparvovec will have a long-term decline in factor levels as has been observed with valoctocogene roxaparvovec, though decline appears to be more gradual, if it occurs at all*”

Section 3.2 Comparative Clinical Effectiveness: Uncertainties and Controversies

In addition to the above comment, CSL Behring has concerns about the statement: “*Finally, the long-term impact of the therapy on liver function and the potential for oncogenesis remain a concern*”. First, we note that AAV5 mediates expression primarily from episomes and has a low probability of chromosomal DNA insertion, which reduces the risk of insertional oncogenesis.⁹ Long-term evaluations of patients with AAV gene therapies for over ten years have failed to demonstrate any gene therapy-induced oncogenesis.^{10; 11} We acknowledge that there was one patient in the HOPE-B trial that developed hepatocellular carcinoma (HCC). However, as ICER notes, this was considered not related to treatment. This assessment was made by independent molecular tumor characterization and vector integration analysis. As noted in a recent press release: “*AAV vector integration in the patient’s tissue sample was extremely rare and accounted for 0.027% of the cells*

in the sample. The integration events were distributed randomly across the genome, and there was no evidence of clonal expansion or any dominant integration event. Additionally, whole genome sequencing of the tumor confirmed that the patient had several genetic mutations that are characteristic of HCC and are independent of vector integration. Finally, gene expression analysis of the tumor and adjacent tissue suggested a precancerous state in the liver consistent with several risk factors that predispose this patient to HCC.”¹² Taken together, the investigation strongly suggests that etranacogene dezaparvovec did not contribute to this particular case of HCC and it is unclear on what other basis the potential for oncogenesis remains a concern. Therefore, we recommend amending the statement to remove the clause around potential for oncogenesis or for ICER to elaborate more clearly on their rationale for this statement

Section 3.3 Comparative Clinical Effectiveness: Summary and Comment

In their review framework, ICER cite etranacogene dezaparvovec as having a B+ rating. This indicates “... *that there is moderate certainty of a small or substantial health benefit with high certainty of at least a small net health benefit (B+) for etranacogene dezaparvovec compared with factor IX prophylaxis*”¹ In this review, ICER notes that causes for uncertainty include uncontrolled study design, small patient numbers and relatively short follow-up time. The HOPE-B trial design followed the Food and Drug Administration (FDA)’s Guidance for Industry on human gene therapy for hemophilia.¹³ The six-month lead-in data collection on annualized bleeding rate (ABR) on optimized prophylaxis allowed for within-subject comparison, which the FDA notes “*increas[es] the statistical power relative to a design with parallel control.*”¹³ We acknowledge that the HOPE-B trial did not have as many patients as phase 3 trials for non-rare conditions, but we note that the number enrolled is greater than a typical rare disease trial and note that the trial was sufficiently powered to draw conclusions.^{4; 14} We are also unclear on what relative criteria ICER concludes that HOPE-B had “*relatively short follow-up*”. Data provided to ICER academic-in-confidence had follow-up that met the FDA’s Guidance for Industry criteria for “Long-Term Monitoring”.¹³ The HOPE-B trial is planned with at least five years of follow-up which should serve to reduce extrapolation-related uncertainty in the future.¹⁵ However, waiting until the full five-year data cut rather than evaluating using the current data would require PWHB to wait for over an additional three years for a therapy that has already firmly established superior efficacy.

More broadly, we disagree that there is only moderate certainty that etranacogene dezaparvovec will provide a substantial health benefit, as it is our position that the HOPE-B trial demonstrates a substantial health benefit in and of itself. As this data is empirically demonstrated, it provides high certainty of a substantial health benefit. As ICER noted, the majority of patients within HOPE-B who completed administration of etranacogene dezaparvovec were able to discontinue FIX prophylaxis for least eighteen months. When considering only patients that would match the expected label indication restrictions for baseline anti-AABV titers, 100% of patients that received a full dose etranacogene dezaparvovec were able to discontinue FIX prophylaxis therapy. This is *per se* a net health benefit, by reducing the burden of self-infusions which directly contributes to quality of life of PWHB and their caregivers.^{16; 17} The benefit of treatment extended beyond prophylaxis discontinuation; patients had highly statistically significant improvement in ABR after receiving etranacogene dezaparvovec. Treated ABR was 3.65 during the six-month lead-in and 0.84 at months 7-18 post-dose (rate ratio [RR] = 0.23, $p < 0.0001$) and treated joint ABR was 2.13 during the six-month lead-in and 0.44 during months 7-18 post-dose (RR = 0.20, $p < 0.0001$). Over one year on average, this represents over 2.5 fewer treated bleeds per patient, and over 1.5 fewer treated joint bleeds per patient. Clinical benefits translated into improvements in quality of life as measured by

the Haem-A-QoL Total, and Feelings, Treatment, Work/School, and Future subdomains. While a “substantial health benefit” is a subjective assessment, our position is that eliminating prophylaxis, reducing ABR to the magnitude seen within HOPE-B, and improving patient quality of life for over one year is sufficient to constitute a substantial health benefit. Additionally, the stability of the AMT-060 precursor for five years is strongly suggestive that clinical improvements would persist for at least five years.⁸ We would ask ICER to reconsider, or more clearly explain the criteria for determining the magnitude of health benefits for future reviews.

Despite these minor concerns, CSL Behring appreciates the thought and effort that went into ICER’s review of etranacogene dezaparvovec. We agree with the conclusions that ICER has drawn about the great potential for this gene therapy to not only reduce bleeding episodes and subsequent complications, but also provide substantial cost offsets at ICER’s chosen list price. CSL Behring welcomes this feedback period, ICER’s transparency, and ICER’s use of the best available data to draw conclusions. We look forward to re-assessing these analyses when we have more follow-up data from the HOPE-B trial which will allow for an even more definitive demonstration of the value of etranacogene dezaparvovec. Overall, we find this report to offer valuable support in our mission to improve the lives of PWHB through a one-time therapy that can eliminate FIX infusions for prophylaxis, significantly reduce bleeds, and substantially reduce the cost burden on the health care system.

Sincerely,

Robert R. Rouse
Head of US Market Access
CSL Behring

References

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October 11, 2022

Institute for Clinical and Economic Review (ICER)
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Dear ICER Review Panel,

Genentech, a member of the Roche Group, appreciates the opportunity to make recommendations about, *Draft Evidence Report: Gene Therapy for Hemophilia B and An Update on Gene Therapy for Hemophilia A: Effectiveness and Value* [1]. We are committed to engaging with ICER to support a final report that objectively informs healthcare decision-makers about the clinical and economic value of valoctocogene roxaparvovec relative to its comparators.

While we agree with the draft clinical assessment, we urge ICER to address problems with the methodologic approach to the economic assessment. Most notably, ICER opted to continue using an outdated economic model based on a natural history study published over 10 years ago [2], rather than make full use of all available phase 3 clinical trial data [3-8] with long-term outcomes. We highlight problems with the economic assessment in pursuit of a goal that we share with ICER, to support fair access [9] to therapies for persons with hemophilia A (PwHA).

Acknowledging that the Evidence Report is being finalized, we urge ICER to consider the following recommendations:

- 1) Revise the economic assessment to make full use of the available clinical trial evidence, or at minimum, state the results in context to the limitations of the data that was used.**
- 2) Quantify and describe uncertainty in the economic assessment, or at minimum, state results in context to assumptions about the treatment response and duration of effect.**
- 3) Apply current clinical practice guidelines to the economic assessment by revising, or at least, testing assumptions that were made about the re-initiation of prophylaxis after valoctocogene roxaparvovec.**

We further expand on these recommendations with supporting rationale and implications below:

- 1) Revise the economic assessment to make full use of the available clinical trial evidence, or at minimum, state the results in context to the limitations of the data that was used.***

Recommendations: Update the efficacy inputs in the economic model to make full use of the GENER8-1 trial outcomes, including annualized bleed rates (ABR), among the defined population of PwHA previously receiving factor VIII (FVIII) prophylaxis.

Rationale: A health technology assessment should be based on evidence of a product's clinical efficacy. The cost-effectiveness model should be built upon the highest level of clinical evidence [10-13]. As the hierarchy of evidence dictates, level one evidence from clinical trials should preferentially be applied as parameter estimates over data from natural history studies [14]. For this assessment, ABR outcomes from the GENER8-1 trial should be used to model patient outcomes instead of using FVIII activity levels from a natural history study [2]. The approach that ICER chose based on the aforementioned natural history study, would lead to a clinically significant *underestimation* of bleeding events compared to simply applying GENER8-1 trial outcomes. For example, among the subgroup of 13 PwHA in the GENER8-1 trial who had *worse* outcomes 6 months after valoctocogene roxaparvovec [5], the actual mean ABR was approximately 5 bleeds per year. Whereas, the approach that ICER described would have resulted in an estimated ABR of 2 bleeds per year.

Another important problem to consider is the lack of clinical trial evidence comparing valoctocogene roxaparvovec to emicizumab. Clinical trial evidence from the GENER8-1 trial provides evidence to support a comparison between FVIII prophylaxis and valoctocogene roxaparvovec [5]. Unfortunately, ICER's economic assessment does not make use of the available comparative clinical data. Without FVIII as a treatment option in this economic assessment, the common comparator between emicizumab and valoctocogene roxaparvovec is missing, precluding a rigorous indirect comparison. ICER's own clinical assessment concluded the same, that there was insufficient evidence to make a comparison between emicizumab and valoctocogene roxaparvovec. This should be accounted for in the results of the economic assessment.

Indirect treatment comparisons also require that populations across studies be reasonably comparable, with similar inclusion and exclusion criteria [15]. Populations treated in emicizumab trials [7,8,16,17] are substantially different from PwHA treated in the GENER8-1 trial [5]. These limitations should be explicit in ICER's economic assessment.

Implications: Failure to make full use of the GENER8-1 trial evidence leads to an economic assessment that relies too heavily on assumptions and places insufficient weight on the current evidence available, leading to an inaccurate conclusion about the relative value of valoctocogene roxaparvovec.

2) *Quantify and describe uncertainty in the economic assessment, or at minimum, state results in context to assumptions about the treatment response and duration of effect.*

Recommendations: ICER should (A) describe the economic impact of uncertainty about treatment durability; (B) more accurately capture the heterogeneity of the patient journeys seen in the GENER8-1 trial through more robust sensitivity analyses, instead of relying on averages that fail to describe the range of observed experiences with valoctocogene roxaparvovec; (C) align the economic assessment results with those of the clinical assessment, or at least provide more transparency around the misalignment between the clinical and economic assessments.

Rationale: Due to the limited durability of gene therapy over a lifetime horizon, it would not be a viable option to make an economic comparison between emicizumab versus valoctocogene roxaparvovec *alone*. At the core of the economic assessment, the draft evidence report presents

“Results for the Base-Case for Valoctocogene Roxaparvovec Compared to Emicizumab” [1]. However, the economic assessment actually compares emicizumab alone to the implicit sequence of *valoctocogene roxaparvovec followed by emicizumab*. Based on model assumptions that ICER applied in their economic assessment, *100% of patients who received valoctocogene roxaparvovec would eventually initiate emicizumab* after 12 years (cycle 24) due to low FVIII activity (<1 IU/mL). From a modeling perspective, the inclusion of subsequent therapy constitutes “sequential therapy” rather than “monotherapy”. When PwHA who are not “cured” after valoctocogene roxaparvovec then receive additional prophylaxis, over a lifetime they have experienced the costs and effects of *both* therapies.

Additionally, while the GENE8-1 trial data supports ICER’s prediction that all PwHA receiving valoctocogene roxaparvovec would eventually require re-initiation of prophylaxis, we disagree with the assumption of an “average” patient journey including re-initiation of prophylaxis after 12 years. Such an assumption does not account for the heterogeneity in the treatment effect of valoctocogene roxaparvovec, observed in the clinical trials [5,18]. Over 2 years of follow-up after treatment with valoctocogene roxaparvovec, 5% of trial participants re-initiated prophylaxis, with at least 24% of all trial patients having FVIII levels in the moderate to severe range [18]. Therefore, at the very least, sensitivity analyses should incorporate the full range of these heterogeneous patient experiences with valoctocogene roxaparvovec to better reflect the uncertainty related to outcomes.

Furthermore, we disagree with ICER’s approach to address uncertainty by applying base-case assumptions that align with a value-based contract proposed by BioMarin, which excluded data on patients with high ABRs after receiving valoctocogene roxaparvovec [1]. Since value-based contracts are confidential agreements between manufacturers and payers, there is *no transparency* about the net financial impact of these contracts, and they *do not* constitute evidence to inform an objective economic assessment. Applying an assumption that aligned with the aforementioned value-based contract could bias the economic results in favor of valoctocogene roxaparvovec, overstating the benefits of the new therapy.

The draft clinical assessment accounted for uncertainty related to the heterogeneity in patient experiences, however the draft economic assessment did not [1]. Unless the economic assessment is updated to align with the clinical assessment, there remains a disconnect between the clinical and economic assessments, which should be clearly explained in the executive summary.

In the economic assessment, ICER reported valoctocogene roxaparvovec to be dominant versus emicizumab, even though the clinical comparative-effectiveness analysis determined that there was insufficient evidence to draw a conclusion [1]. The clinical assessment underscored the high uncertainty due to multiple factors (e.g., uncontrolled trial design with small numbers of patients in the studies, relatively short follow up periods, lack of long-term understanding of net benefits and impact on liver function and risk of hepatocellular carcinoma). At present, the excessive clinical uncertainty discussed in the clinical review is almost entirely absent from the economic assessment, leading to conclusions about dominance that can easily be misinterpreted by the healthcare decision-makers that are the end users of the evidence report. Furthermore, the face validity of the economic assessment appears misaligned with the uncertainty in the clinical assessment, as every probabilistic sensitivity analysis (PSA) ended in the same outcome. Such

results suggest that the PSAs are not capturing the key issues that need to be explored through more robust sensitivity and scenario analyses.

Given the adeno-associated virus (AAV) mechanism of action of valoctocogene roxaparvovec, it is important to note that PwHA only have one opportunity to take an AAV gene therapy. As recently stated in a review by Drs. Samelson-Jones and George, “Potential recipients will need to fully understand that they can receive AAV gene therapy only once, and the loss of transgene expression of FVIII must be considered in their risk/benefit calculus” [19].

Implications: As PwHA will likely only have one opportunity to receive a gene therapy, it is vital that ICER present results clearly, and with appropriate context about the uncertainty, to support informed decision-making that accounts for all relevant information. Without addressing the limited durability of valoctocogene roxaparvovec and the heterogeneity of patient experiences, readers of this assessment could easily misinterpret the economic results as depicting a lifetime cure that eliminates the need for future prophylaxis.

Similarly, the large discrepancy between the clinical assessment and economic analysis may cause healthcare decision-makers to question the validity of ICER’s dominant economic result. Stakeholders may misinterpret these mixed results, which could lead to negative consequences with regard to patients’ access to therapies.

3) *Apply current clinical practice guidelines to the economic assessment by revising, or at least, testing assumptions that were made about the re-initiation of prophylaxis after valoctocogene roxaparvovec.*

Recommendations: (A) Define a cure versus a treatment failure after valoctocogene roxaparvovec based on guideline-concordant [20] need for prophylaxis, using FVIII activity levels and ABRs reported in the GENE8-1 trial. (B) At the very least, ICER should state the economic results with respect to the assumptions that were made about re-initiation of prophylaxis.

Rationale: The economic assessment involved assumptions related to re-initiation of prophylaxis that do not reflect the current standard of care. According to the World Hemophilia Federation (WFH) [20], recommendations on prophylaxis include the following:

“ For patients with hemophilia A or B with a severe phenotype (note that this may include patients with moderate hemophilia with a severe phenotype), the WFH strongly recommends that such patients be on prophylaxis sufficient to prevent bleeds at all times, but that prophylaxis should be individualized, taking into consideration patient bleeding phenotype, joint status, individual pharmacokinetics, and patient self-assessment and preference.”

Despite the guidelines recommending sufficient prophylaxis to prevent **all** bleeds, the ICER economic assessment assumes that re-initiation of prophylaxis occurs after a projected 7 bleeding events annually [1], which is excessive, unrealistic, and unethical. Additionally, the guidelines state that PwHA with a severe phenotype (which could include low FVIII or high ABR criteria) should be offered prophylaxis to target a trough FVIII level of 3-5% [20]. However, ICER seems

to require a FVIII level <1% to model re-initiation of prophylaxis [1]. Notably, emicizumab prophylaxis is reported to meet FVIII level equivalence of >10% in those receiving therapy [21,22]. The gap between ICER's assumptions and the current clinical practice warrants testing different assumptions about re-initiation of prophylaxis after valoctocogene roxaparvovec (e.g., under different thresholds of FVIII levels and ABRs), to better reflect current practice and the individualized approach recommended by the clinical guidelines.

Another important problem with the current assumptions underlying the draft economic assessment relate to the current options for hemophilia A prophylaxis, which include FVIII products as well as emicizumab. Given the real-world prophylaxis utilization rates, ICER should include FVIII replacement products as an option for prophylaxis after failure of valoctocogene roxaparvovec, rather than limiting prophylaxis only to emicizumab. In the American Thrombosis and Hemostasis Network (ATHN) registry, 46% of the participating PwHA without inhibitors used emicizumab, while 28% infused standard half-life (SHL) FVIII products, and 18% utilized an extended half-life (EHL) recombinant factor concentrate for prophylaxis [23]. The ATHN data demonstrates that the WFH guidelines have been incorporated into current practice, showing how "prophylaxis should be individualized" [5]. It is imperative that the real-world options for hemophilia A prophylaxis are included in the assessment to reflect the current treatment landscape and clinical guideline recommendations.

Implications: If ICER does not apply the current guidelines and model real-world scenarios for initiation of prophylaxis, the economic assessment will overestimate the efficacy and durability of valoctocogene roxaparvovec, and substantially underestimate the lifetime costs. Additionally, if ICER does not account for the current standard of care and treatment options for prophylaxis, the resulting economic assessment will not reflect the reality that PwHA and healthcare decision-makers face. Ultimately, this oversight could result in misinformed decisions about access to therapies and pricing negotiations that could negatively impact patients. ICER has an obligation to prevent such misunderstandings and ensure fair access to treatment for PwHA.

Conclusion

Across all of our recommendations, a consistent request is that ICER support evidence-based decisions that utilize the relevant data from clinical trials and reflect the current standard of care. People with hemophilia A face many challenges when trying to access the treatments they need. Due to the high costs of treating this rare disease, payers are increasingly managing therapies for hemophilia A. As a leader in developing transformative therapies for hemophilia A, we are committed to advancing access to innovative therapeutic options for PwHA. Paramount to this advancement of access is the necessity for evidence-based decision-making and transparency around uncertainty. We hope that ICER will see this letter as supporting our commitment and welcome the opportunity to discuss our concerns in further detail.

Sincerely,

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9 October 2022

Dear Dr Pearson

GENE THERAPY FOR HEMOPHILIA B AND AN UPDATE ON GENE THERAPY FOR HEMOPHILIA A: EFFECTIVENESS AND VALUE

I refer to your recently released Draft Evidence Report on gene therapy for Hemophilia B and an update on gene therapy for Hemophilia A: Effectiveness and value¹. As stated, the aim of ICER's analysis is to evaluate by the construction of assumption driven simulations for (i) the lifetime cost-effectiveness of using etranacogene dezaparvovec relative to prophylaxis with factor IX in patients with hemophilia B without inhibitors who are eligible for prophylactic treatment and (ii) the lifetime cost effectiveness of using valoctocogene roxaparvovec relative to treatment with emicizumab in patients with hemophilia A without inhibitors who are eligible for prophylactic treatment. It is important to note that assumption driven simulated value claims for cost-effectiveness are not only entirely imaginary and, by definition, non-evaluable but rest on assumptions regarding preference scores and QALYs that are mathematically impossible². While such models are a standard in health technology assessment, they are singular failures; none produce empirically evaluable claims. They are focused on blanket claims for cost-effectiveness that are impossible to empirically evaluate. So much for Popper's concept of objective knowledge and the evolution of our understanding of hemophilia interventions³.

As you will no doubt recall from previous correspondence, you are aware of my concerns that the ICER reference case framework for value assessment fails to meet the standards of normal science⁴. That is, your reports lack credibility in the claims made for the value of products; they cannot be evaluated empirically nor can the claims be replicated. Your models also violate the fundamental axioms of modern measurement theory in confusing ordinal scales with interval and ratio scales. While you might view these reports and the application of lifetime incremental cost-per-QALY calculations and the application of cost-per-QALY thresholds as the state of the art in health technology assessment, the problem is that the entire exercise is essentially a waste of time. This has been detailed in two recent publications in F1000Research (you might consult the peer reviews, all of which were favorable) which have addressed the manifest deficiencies in the CHEERS 22 guidance for constructing imaginary worlds, described as the ISPOR/ICER meme or belief system for inventing (non-evaluable by design) value claims for cost-effectiveness and the

possibility of systematic bias in sponsored model claims^{5 6 7}. Your assumption driven simulation models and their imaginary claims are an analytical dead-end.

A further point is that your model cannot claim to be ‘superior’ to other models as there is no basis for making a claim that one set of assumptions is ‘more realistic’ than another; you fail to recognize Hume’s problem of induction (first put forward in 1748). Any model can be reverse engineered to create ‘desirable’ claims; this applies, in particular, to the application (incorrectly) of utilities to create QALYs⁶. I know you and your academic advisers are steadfast in your belief (‘have confidence’) that multiattribute utilities have ratio measurement properties (you should claim bounded ratio properties); you never provide a proof (because it is impossible)⁸. The preferences or utilities are composite ordinal scores. Perhaps you might demonstrate that the EQ-5D-3L (which features in the hemophilia modeled imaginary claims) has ratio properties for a single attribute?

I would like to pursue in a little more detail the use of the EQ-5D-3L ordinal preference scores in your imaginary model simulation. The first question is whether or not you or your academic advisers undertook a systematic review of the use of preference instruments and quality of life scores in hemophilia A and B? There is a significant literature, but you only cite six papers^{9 10 11 12 13 14}. Indeed, you fail to point out that the Ballal et al EQ-5D-3L scores are simulated EQ-5D scores for a typical patient with and without knee surgery and the Fischer reference is for the SF-36. More discussion here would help the reader as to why you selected the EQ-5D-3L; apart from its application in your previous study report¹⁵ (and my critique¹⁶).

It has been noted on a number of occasions that the EQ-5D-3L is ill-suited as an ordinal preference measure for modeling and the creation of impossible QALYs. A recent paper by Xu et al note that the EQ-5D may not be able to detect certain changes in HRQoL due to symptoms unique to hemophilia or side effects resulting from its treatment; hence they propose, unwisely, a bolt on methodology for condition specific items to capture better the needs of patients¹⁷. Note that they utilize the EQ-5D-5L; is there any reason why you stay with the now historic EQ-5D-3L? The application of the EQ-5D-3L and its lack of sensitivity in patients with hemophilia has been noted by other authors. O’Hara et al note that across all five dimensions of the EQ-5D-3L the majority of patients reported no problems, with fewer than one in ten patients reporting extreme problems in any dimension¹³. For the few extreme problems reported, pain/discomfort and anxiety/depression were the most common dimensions. It should be noted that as these 3 response levels in the EQ-5D-3L are ranked ordinal responses, the psychometric distance between the various pairs is unknown. The same issue arises with the EQ-5D-5L. Given the ordinal responses (note also that TTO scores are ordinal) it is impossible to see how these can result in an EQ-5D-3L algorithm to produce a ratio scale. Of course, if the majority of hemophilia patients report no problems, claims for any meaningful change in preference or utility would be minimal which means unit prices will dominate imaginary cost-per-QALY claims, supporting threshold criteria for price reductions. In your model you produce imaginary lifetime QALYs that only differ by 0.67 years (17.98 vs. 17.31; Table 4.3)

A commitment to inventing value claims with assumption driven simulations must recognize, and accept, that if assumptions are varied, imaginary value claims will change. Consider, as an example, the choice of the SF-6D instead of the EQ-5D-5L in hemophilia. An evaluation of their psychometric properties found that while both are significantly correlated with the ordinal scores

of the Haem-A-QoL (see below) they should not be considered ‘equivalent’ due to their poor agreement and differing discriminatory power¹⁸.

Perhaps the most comprehensive assessment of the variability in reported utility scores is the Carroll et al study for France and the UK¹⁹. Applying four instruments to hemophilia populations in each country they found significant variations in the scores reported for the EQ-5D-3L, EQ-5D-5L, SF-6D and the SF36. The authors caution that while each instrument shows similar trends, each led to unique values: In general, the EQ-5D-5L gave higher values than the EQ-5D-3L, while the SF-6D was localized within a small range compared to these two instruments. It would have been useful for ICER to assess studies such as this one, pointing out that the SF-36 has been used widely in hemophilia populations^{20 21}. Unfortunately, none of the papers cited made any reference to the measurement properties of the instruments. The obvious conclusion is that the varied applications will yield a range of imaginary modeled value claims. Which to choose (if any)?

It is also worth noting that the disease specific, Likert-scale based, Haem-A-QoL (adult) and Haemo-QoL (children and adolescent) instruments for hemophilia produce only composite, ordinal scores²². They cannot be applied to assess either health status or response to therapy. This means that efforts to map from the Haem-A-QoL to the EQ-5D-5L are a waste of time²³. As far as can be ascertained no attempt has been made to evaluate these instruments in terms of the Rasch measurement model; e.g., applying the Rasch Rating Scale Model to evaluate their approximation to an interval score⁸. This failure in disease specific QoL in hemophilia mirrors the failure with the generic EQ-5D-3L/5L instruments. There is, of course, a solution: to develop disease specific instruments for adults, adolescents and caregivers in terms of the single needs-fulfillment attribute; to develop from first principles instruments that meet Rasch or modern measurement theory standards which provide empirically evaluable value claims for therapy responses, based on interval measures. Presumably this would be asking too much. Even so, it is important to note that there is an extensive literature and recommendations for outcomes measures in hemophilia which should be addressed if a comprehensive picture of empirically evaluable outcomes is to be presented instead of the limited generic instrument favored by ICER; these include, as you note in passing, recommendations specific to gene therapy^{24 25}.

Finally, to return to the claim for an analytical dead end: none of your value claims for these products are empirically evaluable; none meet the standards for Rasch or modern measurement theory. They should play no part in formulary decision making. They are only one set of non-evaluable claims among a myriad of other for alternative assumption driven models. There is no basis, therefore, for progress in terms of discovering new facts from a research strategy and protocol driven claims, as well as outcomes-based contracting in hemophilia

Yours sincerely

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October 11, 2022

Institute for Clinical and Economic Review
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Re: Draft Evidence Report ICER 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 Evidence Report for valoctocogene roxaparvovec for hemophilia A and etranacogene dezaparvovec for hemophilia B.

We are pleased to submit the following comments, which amplify points raised in prior submissions during earlier input periods. The comments below are relevant both for the Final Evidence Report, as well as the policy roundtable discussions to be held during the public meeting.

First, thank you for taking into consideration our prior recommendations relative to several key patient important outcomes: inclusion of health utility within the model; and discussion of the differing adverse event profiles of the two gene therapies under review, in particular the frequency of transaminitis leading to a prolonged duration of corticosteroid therapy.

Financial Toxicity / Health Benefit Price Benchmarks: Given the existing high life-time cost of hemophilia treatment, it is not surprising that gene therapies for both hemophilia A and B were deemed dominant and cost effective at a placeholder price of \$2.5 million. As ICER has noted and we have agreed during prior hemophilia reviews, the current cost of hemophilia treatment is “financially toxic” for PwH, their families, and the health care systems on which they depend. The finding that gene therapy is cost effective does not mean it is affordable, that it will be accessible within the marketplace post-approval, or that it is an optimal treatment for every eligible patient. We remain concerned that high target prices will impede access to these potentially transformative therapies.

Considering these concerns, we call ICER’s attention to a recent Biomarin investor call held following the EU conditional approval of valoctocogene roxaparvovec for hemophilia A held on August 24, 2022¹. In this call, a “first year free pricing” launch price of 1.5 million euros net of all discounts and reserves was indicated for Germany (the expected initial market). Other EU pricing has not yet been announced but is anticipated this month. Taking into account the “financial toxicity” of currently available treatments, we caution against gene therapy pricing in the US being justified based on a multiple of the current treatment cost. While there are notable differences between US and European health systems

¹ <https://investors.biomarin.com/2022-08-24-First-Gene-Therapy-for-Adults-with-Severe-Hemophilia-A,-BioMarins-ROCTAVIAN-TM-valoctocogene-roxaparvovec,-Approved-by-European-Commission-EC>.

and their respective current market prices for current therapies, the net resulting German price of 1.5 million euros is useful as a reference point for the Health Benefit Price Benchmarks discussion included in the final report.

Risk Mitigation: In the last full paragraph on page 2 of the Background, to be clearer, we suggest the last sentence commenting on the approval of valoctocogene roxaparvovec in Europe (“Valoctocogene roxaparvovec was approved for the treatment of severe hemophilia A adults on August 24, 2022, by the European Commission.”) be moved to the end of the prior paragraph and not be part of the paragraph discussing etranacogene dezaparvovec. Further, we would suggest this sentence be revised to reflect the conditional nature of the approval as follows: “Valoctocogene roxaparvovec *received conditional market authorization with requirements for additional monitoring* for the treatment of severe hemophilia A adults on August 24, 2022, by the European Commission.”

This EU authorization and mandatory risk management requirements are consistent with the recent National Hemophilia Foundation Citizen’s Petition requesting that, if the FDA approves a hemophilia gene therapy in the United States, the Agency should require a rigorous risk evaluation and mitigation strategy (REMS) to ensure the health and well-being of PwH who receive a gene therapy product.²

Disability Paradox / Health Utility: Thank you for recognizing the “disability paradox” and resulting limitations of population-based health measures, and for responding to our request for the inclusion of a utility gain within the assessment. Although based on the generic EQ-5D-5L, the inclusion of this perspective provides a notable patient-centric improvement over prior hemophilia reviews and the earlier draft Modeling Analysis Plan for this review. We also agree, as noted by ICER on page 3, that the psychosocial impact of hemophilia for both PwH and their caregivers is enormous. The current model does not capture the potential transformation in mental health outlook when a “hemophilia-free mindset” is achieved.³ Similarly, we agree with the observation on page 5 that the currently available outcome data sets do not yet capture this transformation. We are working to resolve this limitation in outcomes research for PwH and look forward to its consideration in future value assessments.⁴ As we have consistently advocated, there are many important outcomes, including a change in psychosocial status, important to PwH beyond a low annual bleed rate or changed joint health score as used in the model. Inclusion of the health utility gain is a positive and welcome step, though we will continue our requests that ICER utilize a hemophilia-specific health utility measure fully incorporating outcomes important to PwH.

Step Therapy / Return to Prophylaxis: As noted above, we remain concerned about our community’s ability to access innovative therapies due to the cost of treatment and the insurance barriers they face. In ICER’s prior hemophilia review (November 2020), it reported several policy recommendations that are important for the current review:

- *Payers considering implementing formal step therapy, however, should recognize the heterogeneity of patient experience with factor VIII and its different delivery mechanism.*
- *Payers should cover factor VIII prophylaxis at levels adequate to achieve higher troughs than*

² <https://www.regulations.gov/docket/FDA-2022-P-1444>. While NHF filed the initial Citizens Petition, supportive comments have been made by the Hemophilia Federation of America and the European Haemophilia Consortium.

³ Krumb, E, Hermans, C. Living with a “hemophilia-free mind” – The new ambition of hemophilia care? *Res Pract Thromb Haemost.* 2021; 5:e12567. <https://doi.org/10.1002/rth2.12567>

⁴ Clearfield E, Chang HY, Messner D, Valentino LA, Skinner M. Development of a Patient-Reported Outcome Measure (PROM) to Fully Report a Proposed Core Outcome Set. PCR45, 2022-05, ISPOR 2022, Washington, DC, USA. <https://www.ispor.org/heor-resources/presentations-database/presentation/intl2022-3460/115854>

the 1% level used in the past. - All payers should be aware of the widespread consensus among clinical experts and patient organizations that a trough factor VIII level of 3%-5% should be viewed as a minimum target for the vast majority of patients.

The decision whether or not to undergo gene therapy should remain with the PwH and their health care providers. We oppose barriers that threaten this shared decision-making, such as step therapy through and failure on emicizumab prior to accessing valoctocogene roxaparvovec. Besides impeding access for those for whom gene therapy is the preferred option, there are also several unresolved clinical challenges, including how best to transition from a non-factor replacement therapy with a 30+ day half-life (e.g., whether a wash out period is required), laboratory monitoring,⁵ and potential lifestyle modifications required for PwH during transition to gene therapy if they were required to first switch to emicizumab. For example, people taking clotting factor therapy designed to manage peak FVIII levels for periods of high activity could find themselves forced to switch to a suboptimal product before they could access gene therapy.

Equally, decisions on when a PwH may return to prophylaxis when factor activity levels decline should not be impeded by the construct of a performance-based agreement or requirement that a certain number of bleeding events occur. Thank you for taking note of this community concern on page 5 of the draft evidence report. Here, too, prior ICER recognition on the importance of higher trough levels (3-5% minimum target) remains relevant. This position is also consistent with a recent European consensus statement.⁶ We reiterate our comments submitted as part of the initial scoping for this review on May 25th:

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. 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.

Given the significant decline in factor VIII activity levels over time for recipients of valoctocogene roxaparvovec, it is evident that while the product may provide significant benefit for a period of years, it does not represent a long-term cure. Thus, anticipating an eventual return to prophylaxis is important for those considering this treatment. While we would have a similar concern for hemophilia B, data do not indicate a significant decline in efficacy at this time.

Contextual Considerations and Potential Other Benefits: Within Table 5.2 we offer the following comments:

- The first potential benefit relates to the ability to achieve major life goals. The information here should differentiate between hemophilia A and B. While highly relevant for hemophilia A, the

⁵ Roctavian – EMEA/H.C/005830 Product Information Summary of Product Characteristics (annex 1) page 5. https://www.ema.europa.eu/en/documents/product-information/roctavian-epar-product-information_en.pdf

⁶ Peyvandi, F., Berger, K., Seitz, R., Hilger, A., Hecquet, M.-L., Wierer, M., Buchheit, K.-H., O'Mahony, B., Bok, A., Makris, M., Mansmann, U., Schramm, W., Mannucci, P.M., 2020. Kreuth V initiative: European consensus proposals for treatment of hemophilia using standard products, extended half-life coagulation factor concentrates and non-replacement therapies. *Haematologica* 105, 2038–2043.. doi:10.3324/haematol.2019.242735

comment about needing to pick the right period of life to undergo gene therapy appears less apt for hemophilia B given the durability data to date for etranacogene dezaparvovec.

- The second potential benefit relating to caregiver burden has not captured the significant burden on caregivers for adults. We would refer you to data from the US CHES Study, which quantified a significant economic impact on caregivers for adults with hemophilia.⁷ This estimate was largely derived from caregivers being part-time employed, unemployed or unable to work, due to their care duties preventing them from working more hours.
- The third bullet related to complexity accurately describes prophylaxis. We would also note the significant burden on participants during the first 6- to 12-month period post-gene therapy for laboratory testing, barrier contraception, avoidance of liver toxic substances (e.g., alcohol), and corticosteroid management. A high degree of compliance and adherence is required during this period.
- The fourth bullet relates to health inequities. While it may not be immediately available to all, given the enormous variability in health care coverage in the United States and the significant financial impact (work, career, educational opportunities) hemophilia has on PwH and their families, a durable transformative therapy could have a generational impact that breaks the cycle of economic disadvantage experienced by many in our community.

We appreciate the opportunity to provide these comments and thank you for your consideration. We would be pleased to provide further input or clarifications if required.

Sincerely,



Leonard A. Valentino, M.D.
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Kim Phelan
Chief Operating Officer
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⁷ Burke T, Asghar S, O'Hara J, Sawyer EK, Li N. Clinical, humanistic, and economic burden of severe hemophilia B in the United States: Results from the CHES US and CHES US+ population surveys. *Orphanet J Rare Dis.* 2021 Mar 20;16(1):143. doi: 10.1186/s13023-021-01774-9. PMID: 33743752; PMCID: PMC7981988. Available at: <https://pubmed.ncbi.nlm.nih.gov/33743752/>.

October 11, 2022

Submitted electronically to: Mfrederick@icer.org

Steven D. Pearson, MD, MSc
Institute for Clinical and Economic Review (ICER)
14 Beacon Street, 8th Floor
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RE: ICER's Draft Evidence Report on Gene Therapies 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 rare bleeding disorders, including 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 prophylactic and/or on-demand treatment for hemophilia B³, and one factor VIIa therapy for the treatment of bleeding episodes among patients with hemophilia A or B with inhibitors⁴. Moreover, NN is currently investigating several non-factor hemophilia treatments that have the potential to improve care for patients across hemophilia A and B with or without inhibitors.

Such a wide spectrum of treatments, including NN-approved and investigational therapies along with innovative gene therapies, allows for an individualized approach to patient care management in which an optimal therapeutic pathway is selected. Our hope is that ICER's assessment should not lose sight of the individual patient and the interpretation of ICER's evaluation should not risk compromising patients' ability to receive therapies that best fit their clinical history and lifestyle choices.

After careful review of the draft evidence report, NN provides highlights of our comments to this draft report below along with further clarification for each of our comments in the subsequent section. We encourage ICER to reconsider these points to ensure that the final evidence report is fully representative of the current treatment landscape and existing clinical evidence.

Highlights of NN Comments

- (1) The market basket derived from the HOPE-B clinical trial⁵⁻⁸ is not representative of real-world practice
- (2) Rebinyn should not be grouped with other factor IX products in a single comparator given its differential, and more beneficial, pharmacokinetic (PK) and efficacy profile

- (3) Conservative estimates should be applied to the durability of gene therapy in the absence of long-term clinical evidence

Detailed NN Comments

(1) The market basket derived from the HOPE-B clinical trial is not representative of real-world practice.

The pivotal phase 3 HOPE-B clinical trial evaluated the efficacy and safety of etranacogene dezaparvovec (EtranaDez), an investigational adeno-associated virus five (AAV5)-based gene therapy, among adults with severe or moderately severe hemophilia B⁵⁻⁸. The trial was designed as an open-label, multi-center, multinational, single arm study. The reference therapy was described as prophylactic factor IX replacement therapy used during the 6-month lead-in period prior to treatment with EtranaDez. The primary outcome measure, annualized bleeding rate (ABR), was compared between the lead-in period with prophylactic factor IX replacement therapy and following administration of EtranaDez.

In its cost-effectiveness analysis, ICER determined that clinical effectiveness data for the market basket comparator was derived from the 6-month lead-in period from the HOPE-B trial. The market basket comparator is comprised of Alprolix, BeneFIX, Idelvion, and Rebinyn. There are several concerns with this approach.

1. Key model input data for the comparator's effectiveness was extracted from a small, multinational trial of 56 participants recruited through 35 sites throughout the world, which likely underrepresents a US-only population of heterogeneous patients with hemophilia B.
2. The ABR for the 6-month lead-in period from the HOPE-B trial was 4.19, which was substantially (numerically) higher than the ABRs from the pivotal trials of each therapy in the market basket^{3,9-11}. The substantially higher ABR for the 6-month lead-in period from the HOPE-B trial indicates sample selection bias when applied to ICER's economic model, namely that patients eligible for the HOPE-B trial did not respond well to, or were non-compliant with, prophylactic factor IX products and thus elected to participate in a gene therapy clinical trial. In its draft evidence report, ICER acknowledged that sample selection bias may be present; however, ICER stated that the ABRs observed during the run-in phase of the HOPE-B trial were comparable to those reported in a recent systematic review of ABRs for patients with hemophilia B on prophylactic therapy (Davis 2019)¹². There are two primary issues with ICER's use of Davis 2019 as supportive evidence:
 - a. Davis 2019 includes a comparison of Idelvion to Alprolix, BeneFIX, Ixinity, Refixia (Rebinyn), and Rixubis. It is important to note that ICER's market basket comparator does *not* include Ixinity or Rixubis, limiting the relevance of this publication for comparative purposes.
 - b. Furthermore, Ixinity (mean [SD] ABR: 3.55 [7.15]) and Rixubis (4.26 [5.80]) were associated with two of the highest trial reported mean ABRs among the interventions under study in Davis 2019. A simple average across the remaining

interventions in the publication yields a mean ABR of 2.3, which is substantially lower than the ABR of 4.19 used for the market basket comparator in ICER's model, further refuting the relevance of this publication for comparative purposes.

3. Since Rebinyn was recently approved by the US Food and Drug Administration (FDA) for the routine prophylactic treatment of adult and pediatric patients with hemophilia B¹³, it is unlikely that many patients were treated prophylactically with Rebinyn during the lead-in period of the HOPE-B trial.

ICER's incorporation of HOPE-B trial data for the model comparator has profound implications on its model findings. Notably, in ICER's one-way sensitivity analysis, the model was highly sensitive to bleeding rates associated with the factor IX comparator (i.e., treated target joint bleeds; treated nontarget joint bleeds; joint bleeds); these three parameters were among the top 10 variables that had the largest impact on model results. As currently constructed, a higher ABR for the model comparator inappropriately yields a lower CE ratio in favor of EtranaDez, and specifically a dominant strategy in ICER's current analysis.

Recommendation: ICER should consider conducting scenario analyses using the average ABR across the individual trials of the four therapies comprising the model's market basket of factor IX therapies. Doing so will better reflect the benefits of the current standard of care in the United States today.

(2) Rebinyn should not be grouped with other factor IX products in a single comparator given its differential, and more beneficial, pharmacokinetic (PK) and efficacy profiles

Rebinyn (Nonacog beta pegol) is a glycopegylated recombinant factor IX protein with an extended terminal half-life. In July 2022, the US FDA extended Rebinyn's approval to routine prophylactic treatment to prevent or reduce the frequency of bleeding events in adult and pediatric patients with hemophilia B¹³. The approval was based on data from the main phase of the adult and pediatric previously treated patients (PTP) trials, which demonstrated median ABRs of 1.04, 2.00, and 0 in patients 13 years of age and older, 7 to 12 years of age, and ≤6 years of age, respectively¹³.

Additional clinical trials have been conducted comparing Rebinyn to other factor IX prophylactic therapies. For instance, a phase 1 study comparing 25, 50, and 100 IU/kg doses of Rebinyn to BeneFIX found an approximate five-fold increase in half-life associated with Rebinyn (93 hours for Rebinyn vs. 19 hours for BeneFIX)¹⁴. Moreover, the study found a two-fold increase in recovery rate associated with Rebinyn compared to BeneFIX. A graphical representation of these outcomes follows (**Appendix – Figure 1**).

Similarly, a second phase 1 study comparing a single dose of Rebinyn 50 IU/kg to a single dose of Alprolix 50 IU/kg found a four-fold increase in factor coverage associated with Rebinyn (96.6 IU x h/mL for Rebinyn vs. 22 IU x h/mL for Alprolix)¹⁵. Moreover, the study found that Rebinyn was associated with a two-fold increase in the recovery rate and a six-fold increase in factor levels

at seven days compared to Alprolix. A graphical representation of these outcomes follows (**Appendix – Figure 2**).

These phase 1 studies demonstrate superior clinical properties for Rebinyn compared to interventions even within the same therapeutic class. ICER's aggregation, therefore, of factor IX products in a single market basket comparator ignore the clinical benefits of Rebinyn.

Recommendation: ICER should include separate discussion regarding the benefits of each individual factor IX product, notably Rebinyn, in the summary section of its final evidence report.

(3) Conservative estimates should be applied to the durability of gene therapy in the absence of long-term clinical evidence

Gene therapies in hemophilia B have the potential to reduce or eliminate the need for further prophylactic therapy with factor IX products. In the HOPE-B trial of EtranaDez, nearly all patients discontinued factor IX prophylaxis during the duration of the clinical trial period (i.e., months 7-18); however, evidence of the long-term duration of benefit of this gene therapy beyond the clinical trial duration does not exist. Contrary to this uncertainty, ICER's model assumes a much longer-term durability of treatment associated with EtranaDez before resulting in an increase in ABR (i.e., >20 years). As currently constructed, a lower ABR for EtranaDez maintained for a long period of time prevents (1) increases in pharmacy and direct medical costs and (2) decreases in QALYs, inappropriately yielding a lower CE ratio in favor of EtranaDez, and specifically a dominant strategy in ICER's current analysis.

Instead of applying a liberal assumption to its base case analysis, ICER should take a more conservative approach to modeling the long-term treatment effect of EtranaDez given the lack of evidence in this regard. In fact, in ICER's 2022 evaluation of betibeglogene autotemcel (beti-cel; Zynteglo) for the treatment of beta thalassemia, ICER assumed that a small percentage of patients transitioned from a health state of transfusion independence to a state of transfusion dependence after seven years, citing the uncertainty of long-term durability of beti-cel treatment effect over time¹⁶. More specifically, concerns regarding the limited number of patients (N=32) in the phase 3 trial of beti-cel and the limited duration of data (seven years of data for three patients) led to ICER's conservative assumption. For comparison, the HOPE-B trial of EtranaDez only evaluated 56 patients over 18 months, including a 6-month run-in period; yet ICER does not maintain consistency in its methods in the current hemophilia assessment. Moreover, in published models of gene therapies in hemophilia A, 10% of patients were assumed to fail gene therapies after a short time period (i.e., 4 weeks) and resume prophylactic therapy with factor VIII products^{17,18}.

Recommendation: ICER should incorporate a consistent and more conservative assumption regarding the durability of EtranaDez treatment effect over time given its deep impact on model findings. This more conservative assumption should be considered in the base case analysis, or at the least in scenario analyses, to ensure a more balanced and evidence-based assessment.



The recommendations made above are based on clinical justification, the availability of evidence, and economic modeling practices established by ICER and other health service researchers. We encourage ICER to strongly consider these recommendations in the revised and final evidence reports. Doing so will not only uphold the scientific rigor of this evaluation but more importantly will ensure that the interpretation of ICER's evaluation does not prohibit receipt of therapies that meet the diverse needs and preferences of a heterogeneous patient population.

Sincerely,

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Appendix.

Figure 1. Phase 1 Study Comparing Rebinyn to BeneFIX

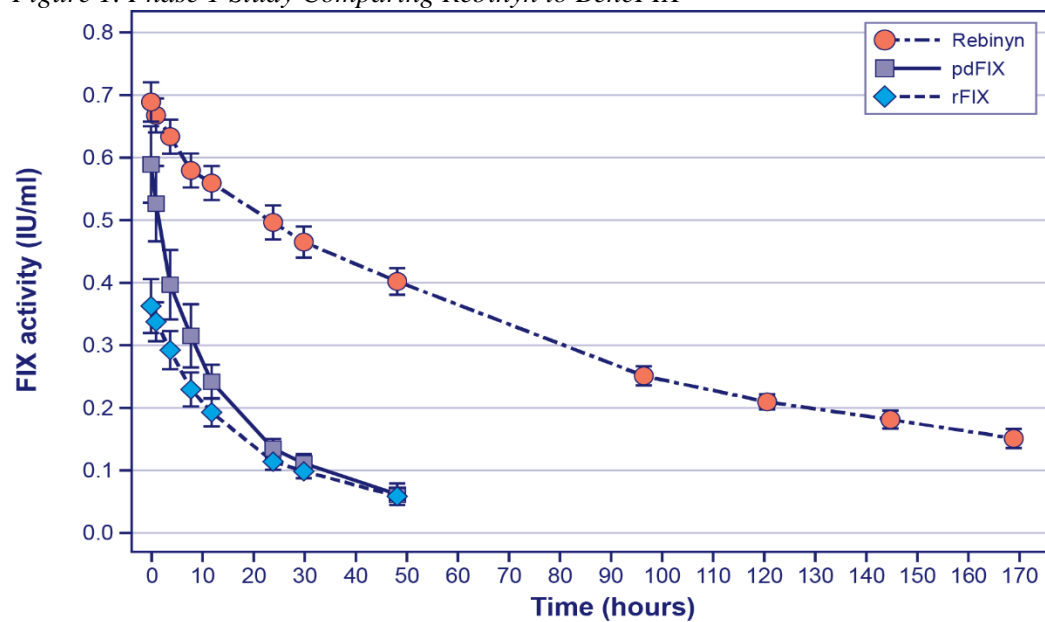
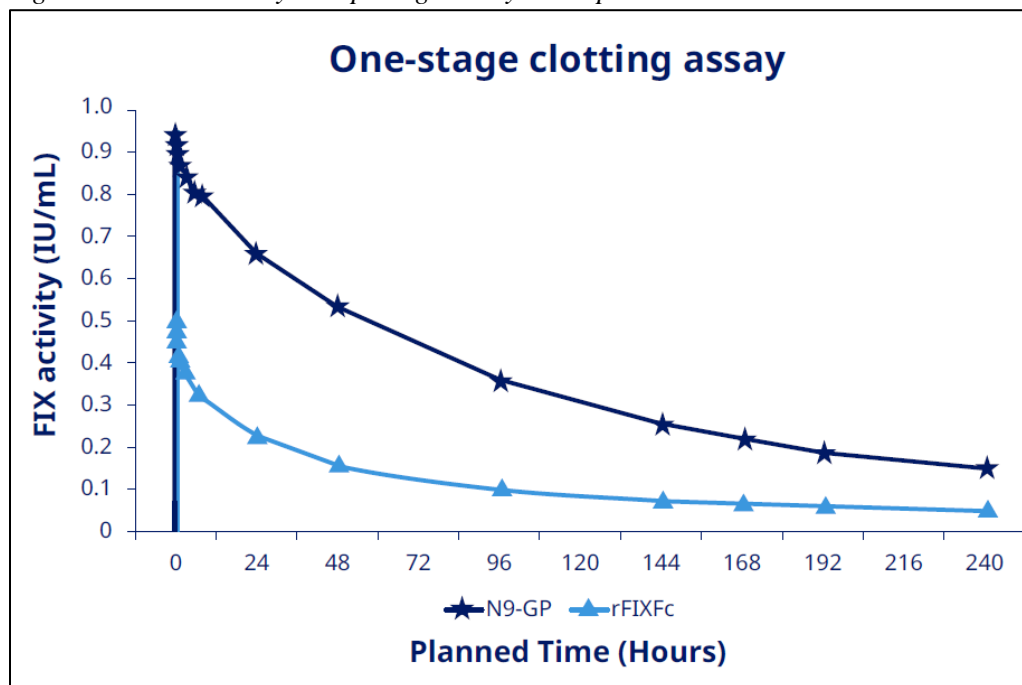


Figure 2. Phase 1 Study Comparing Rebinyn to Alprolix



October 11, 2022

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

Dear Dr. Pearson:

The Partnership to Improve Patient Care (PIPC) appreciates the opportunity to provide feedback on ICER's assessment of treatments for hemophilia B and an update on treatments for hemophilia A.

At the urging of commenters, in the final 2020 report assessing hemophilia treatment, ICER replaced the data for bleed rates and the rate of receipt of Factor VIII with real world data instead of RCT data. The significant impact on the results of the report reflect the significance of each variable and the value of real world data. In this updated report, we provide the following recommendations to ensure the final report better represents value to the patient.

ICER's model oversimplifies the impact of this disease on patients' overall quality of life.

ICER's model is based solely on progression through Pettersson scores, which may be an oversimplification of the impact of hemophilia on patients' quality of life. ICER acknowledges in its report that the burden of hemophilia is not limited to the number of bleeds. Patients also live with uncertainty and chronic pain, which can lead to anxiety, depression, and other mental health challenges. ICER's simplified model is not able to capture these symptoms, particularly as they present in a very heterogeneous manner and are often exacerbated by the fact that access to specialist services in hematology varies wildly based on location, demographics, and insurance coverage.^{1,2}

The health state utilities used are problematic and they likely underestimate the net effect of treatments under review.

There are several issues with the primary source for health utilities in the model that led to the data being oversimplified and unable to generate accurate utilities. These issues include that the three biggest drivers of utility in the Multivariate Poisson distribution are: being in the United Kingdom, age, and target joints (yes or no). The utility set is only varied on age, and a dichotomous proxy of target joints, which has only two states. The number of target joints was a significant driver of the results, so having just two categories is likely too simplistic and may undervalue the effect on quality of life of reducing bleeds.

¹ Hong S, Majhail NS. Increasing access to allotransplants in the United States: the impact of race, geography, and socioeconomics. *Hematology*. 2021 Dec 10;2021(1):275-80.

² Kanter, J., Smith, W.R., Desai, P.C., Treadwell, M., Andemariam, B., Little, J., Nugent, D., Claster, S., Manwani, D.G., Baker, J. and Strouse, J.J., 2020. Building access to care in adult sickle cell disease: defining models of care, essential components, and economic aspects. *Blood Advances*, 4(16), pp.3804-3813.

This data was questioned in a paper by some of the same authors one year later³ who put forward a strong case that the EQ5D results (and hence the health state utility values derived from them) are considerably over-estimated in the Hemophilia A population, as there is considerable evidence of disease-based hedonic adaption⁴ in the patient population. The authors go on to suggest that a preference elicitation study using multiple populations could be used to generate better HSUV for Hemophilia patients in the future.

These findings suggest that the utility values used in the ICER model are underestimates and their use may dilute the full effect of the therapies being evaluated, showing them to be less cost-effective than they are.

The bleed-related disutilities are assumed to apply for just two days. This is an overly conservative assumption and does not reflect the sources being used for these inputs.

The disutility inputs are based on one study involving 37 people, who were followed for 90 days.⁵ Of the patients who completed a diary, they reported 194 bleeding episodes in 90 days; that's just over 5 per patient over 3 months and equates to 10 over the six-month cycle in the model. Yet the model uses a separate source for number of bleeds per cycle. Bleed rates used in models 1 are 4.19, for the standard of care arm, varying by factor level between 0.45 and 7.28 per cycle.

The physical effect of a bleed is rarely limited to two days, and the mental manifestations can last for weeks, so the application for 2 days in the model is not an accurate representation of the patient experience. It also ignores the marginal impact on quality of life from the rate of bleeds over time. The difference between having ten bleeds a cycle and have 1 or 2 bleeds a cycle is considerable from a patient perspective.

The conclusion of the paper from which these inputs are derived states that the results “*indicated that frequent acute bleeds impair QOL beyond patient's non-bleed day baseline.*” This nuance is ignored in the model due to the linear function linking bleed rate and impact on quality of life, underestimating the burden of patients who have multiple bleeds in a short period.

The model assumes no mortality effects.

The model assumes no mortality effects, but presence, severity and treatment burden are all drivers of mortality in Hemophilia so ignoring mortality in a lifetime model does not present an accurate picture.

³ Martin A, Mulhern B, Shaikh A, Asghar S, O'Hara J, Pedra G, Sawyer EK, Li NN. Disease state adaptation experienced by patients with hemophilia: literature review and expert consensus. *Blood*. 2019 Nov 13;134:5801..

⁴ Amundson R. Quality of life, disability, and hedonic psychology. *Journal for the Theory of Social Behaviour*. 2010 Dec;40(4):374-92.

⁵ Neufeld EJ, Recht M, Sabio H, Saxena K, Solem CT, Pickard AS, Gut RZ, Cooper DL. Effect of acute bleeding on daily quality of life assessments in patients with congenital hemophilia with inhibitors and their families: observations from the dosing observational study in hemophilia. *Value in Health*. 2012 Sep 1;15(6):916-25.

ICER's assessment states that as prophylaxis for hemophilia A in patients without inhibitors has not been demonstrated to decrease mortality there should be no mortality effect because of these treatments being studied. This is an oversimplification, as the same paper⁶ suggests that severity of Hemophilia has a strong impact on relative mortality. It states that the mean life expectancy of someone with severe hemophilia is 63 compared to someone with mild or moderate hemophilia of 75. If the severe form of the disease can take 12 years off a patient's life expectancy, then it is highly likely that treatment to alleviate the root cause of the disease and its consequences will result in a lower mortality.

A recent Swedish cohort study based on a long-standing Hemophilia registry showed that the hazard ratio for all-cause mortality for those with Hemophilia A compared with controls was 1.7, ($P < 0.001$) when patients with HIV and/or viral hepatitis were excluded. The corresponding figures for the severe hemophilia subgroup were 6.6, ($P < 0.001$). This occurred even though those with Hemophilia were 57% less likely to die from ischemic heart disease than controls.⁷

There is also evidence of reduced inhibitors being a known risk factor for morbidity. Even though findings were mixed in smaller studies as to their role in mortality, recent larger studies suggest that they are a factor, increasing risk of death by up to 70%.⁸ A similar study suggested a mortality rate five times higher in Hemophilia A patients with inhibitors, than those without.⁹

A model that is assuming no mortality effects from treatments deemed to be 'highly effective' in a disease known to have higher rates of premature death, will underestimate the true value of these therapies.

Conclusion

As we have stated in previous comments, we continue to be concerned about ICER's reliance on the quality-adjusted life year and the equal value of life year gained as metrics for determining cost effectiveness and their implications for ICER's subsequent policy recommendations that may limit access to care regardless of the cost effectiveness conclusions. PIPC appreciates ICER's use of real-world evidence but encourages ICER to revisit some of its modeling choices to ensure that the model accurately reflects value to the patient.

⁶ Darby SC, Kan SW, Spooner RJ, Giangrande PL, Hill FG, Hay CR, Lee CA, Ludlam CA, Williams M. Mortality rates, life expectancy, and causes of death in people with hemophilia A or B in the United Kingdom who were not infected with HIV. *Blood*. 2007 Aug 1;110(3):815-25.

⁷ Lövdahl S, Henriksson KM, Baghaei F, Holmström M, Nilsson JÅ, Berntorp E, Astermark J. Incidence, mortality rates and causes of deaths in haemophilia patients in Sweden. *Haemophilia*. 2013 May;19(3):362-9.

⁸ Walsh CE, Soucie JM, Miller CH, United States Hemophilia Treatment Center Network. Impact of inhibitors on hemophilia mortality in the United States. *American Journal of Hematology*. 2015 May;90(5):400-5.

⁹ Eckhardt CL, Loomans JJ, van Velzen AS, Peters M, Mauser-Bunschoten EP, Schwaab R, Mazzucconi MG, Tagliaferri A, Siegmund B, Reitter-Pfoertner SE, Van Der Bom JG. Inhibitor development and mortality in non-severe hemophilia A. *Journal of Thrombosis and Haemostasis*. 2015 Jul;13(7):1217-25.



PIPC

Partnership to Improve Patient Care

Sincerely,



Tony Coelho
Chairman
Partnership to Improve Patient Care

October 11, 2022
Institute for Clinical and Economic Review
14 Beacon Street, Suite 800
Boston, MA 02108

Re: ICER's Draft evidence report on Gene Therapy for Hemophilia B and An Update on Gene Therapy for Hemophilia A: Effectiveness and Value

To Whom It May Concern:

We appreciate the opportunity to provide comment on the Institute for Clinical & Economic Review (ICER)'s draft evidence report on *Gene Therapy for Hemophilia B and An Update on Gene Therapy for Hemophilia A: Effectiveness and Value*. Sanofi is committed to improving the lives of those affected by these diseases.

Gene therapies represent a novel and significant advance in technology in this space with potential great benefit for patients and their families. However, many uncertainties remain regarding the long-term efficacy and safety of gene therapy in hemophilia that we expect will be resolved by longer-term data collection. We encourage continued evaluation of the impact of gene therapies on safety and long-term factor levels and clinical outcomes in patients with hemophilia.

Long-term safety and efficacy of gene therapies: Given the relatively short duration of clinical data (largely 18-24 months) to date compared to the model timeframe (lifetime) and the fact that a waning effect in efficacy was already shown through decreasing factor levels, especially in Hemophilia A, there is sizeable uncertainty with projecting clinical outcomes to a lifetime. Several other open questions still remain.

- High variability in FVIII levels within dose cohorts were seen in studies so far, signaling possible heterogeneity of response.^{1,2}
- Loss of efficacy was reported in gene therapy trials one to two years after treatment; however, no longer term data exists to inform lifetime effect. For example, in hemophilia A, a phase 3 clinical study of valoctocogene roxaparvovec reported that approximately 12% of participants had factor levels indicative of moderate hemophilia (< 5IU/dL) a year after treatment.²
- There is an unknown potential risk of developing antibodies against factor VIII and FIX once exposure to exogenous factor therapies is initiated, for example, due to the need to treat breakthrough bleeds.
- The report's executive summary mentioned the observed risk of elevated liver enzymes requiring prolonged immunosuppressive therapy with its unknown long-term impact, and the hepatocellular carcinoma risk of gene therapy. While these risks and costs were not integrated into the model or widely discussed subsequently, they are a significant impact and consideration for treatment decision making. The National Hemophilia Foundation (NHF) recently submitted a citizen's petition to the FDA to this effect recommending that

the FDA place a risk evaluation and mitigation strategy (REMS) as a condition of approval to address potential safety concerns.³

- Administration of gene therapy in practice is expected to be burdensome. Extensive screening and testing prior to administration in select specialized and certified centers may be required as well as extensive monitoring during follow up including any needed steroid treatment.

Recommendation: We encourage ICER to further articulate the limitations arising from long-term uncertainty on its findings. This includes the inherent uncertainty of projecting efficacy from existing studies to a lifetime in the context of a one-time treatment with observed waning effect and unknown safety consequences of observed adverse events and the need for steroid use in the long term.

We also recommend that ICER highlight the applicability of model findings in the context of individual patient and doctor risk-benefit assessments specifically within the context of unknown long-term impact. It is vitally important that treatment be determined based on individual patient needs and risk-benefit preferences.

Assumptions on prophylactic restart after gene therapy effect wane: In both hemophilia A and B models, an assumption of treatment re-initiation of prophylaxis only began at projected factor levels between 1 and 5 IU/mL (moderate severity) whereby 5% of gene therapy patients were assumed to switch to prophylaxis treatment. The National Hemophilia Foundation recommends that prophylactic therapy may also be considered for people with hemophilia with moderate and mild hemophilia with a severe phenotype to prevent bleeds. They also recommend that prophylactic therapy should be instituted early (prior to the onset of frequent bleeding). In Hemophilia A, this is supported by observations that higher endogenous FVIII activity levels (well above 5%) is associated with a trend of lower bleeds than factor activity levels between 1 and 3%⁴⁻⁶

Recommendation: Given the long-term uncertainty with factor level projections, need for treatment re-initiation, and data showing factor levels above 5% are associated with reduced bleed -a guideline recommended treatment goal, we recommend that ICER keep ABR as an endpoint (and that patients treated with gene therapy re-start on prophylactic treatment after 5 years as a base case for hemophilia A). Furthermore, we recommend that ICER conduct sensitivity analysis assuming 100% of the gene-therapy-treated patients require prophylactic treatment after 1, 2, 3, 4 and 5 years (for hemophilia A).

Use of Pettersson Score (PS) scores in model structure: The advances in factor and non-factor therapies in the recent years have significantly altered the disease outcomes for patients who are now extensively treated with prophylaxis, and with a greatly reduced need for surgeries. The PS structure widely applied for classification of arthropathy with increasing scores culminating in the need for joint surgery may not be as relevant today. For example, following the draft model assumptions, let us define an annualized joint bleed rate of 1 in a prophylactic-treated hemophilia A population (for simplicity, the life expectancy of each individual is equal to 100 years exactly). Let us also consider the link between joint bleeds and PS (36.52 or 6.52 joint bleeds result in a one-point PS increase in patients aged less or more than 25 years respectively) as well as the link between PS and surgery (a PS of 28 leads to surgery). In this specific population, the average newborn would undergo their first surgery after 392.56 years ($= 25/100 * 1 * 36.52 * 28 + 75/100 * 1 * 6.52 * 28$). This extremely long time to first surgery makes latest stage of PS unlikely on a lifetime prophylactic approach

Recommendation: In patients treated prophylactically, a modelled PS stage is unlikely to result in surgery and hence may not influence the model results much. Nevertheless, it is important to take into account that the on-demand regimen is still widely used with poorer outcomes, higher bleed rates and higher potential for surgery in both Hemophilia A and B. Therefore, we recommend that ICER highlight the rarity of achieving surgical state with new prophylactic or gene therapy treatments.

Budget impact: ICER concluded that the 5-year budget impact expectations did not warrant the creation of a dedicated budget impact model. However, typically payers consider shorter time horizons (often only 1-2 years) in line with their annual budgets.

Recommendation: We would encourage ICER to still comment on the potential affordability and high upfront cost and budget impact implications of gene therapies in the short term. Specifically for smaller US payers, self-funded plans with smaller sizes, or payers who consider budgets on shorter timeframes such as 1-2 years, such budgetary implications and potential need for re-insurance could be of importance.

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 reviews of current and novel therapies.

Sincerely,



Kyle Hvidsten

Head, Specialty Care HEVA
Global Market Access, Sanofi

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