September 22, 2020

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

Dear Colleagues:

Thanks very much for the opportunity to provide comments on the recent draft report "Valoctocogene Roxaparvovec and Emicizumab for Hemophilia A: Effectiveness and Value" on behalf of ourselves as the developers of the cost-effectiveness model published in Cook et al. 2020, which is briefly summarized in the draft report. As disclosed in our publication, our analysis was supported by research funding from BioMarin; however, the analysis and conclusions were our own.

The draft report noted several differences between our modeling approach and the approach that ICER has taken that lead to different conclusions regarding the cost-effectiveness of valoctocogene roxaparvovec. The draft report primarily attributed the differences to (a) the different dose and cost assumptions for Factor VIII (FVIII) prophylaxis, (b) the difference in assumed cost of valoctocogene roxaparvovec, and (c) the disutility associated with regular infusions of FVIII. First, we would like to provide additional thoughts regarding these modeling choices; second, we would like to highlight two additional differences between our modeling approach and that presented in the draft report that may substantially affect the assessment of cost-effectiveness.

In identifying model inputs for FVIII dose, we felt that matching real-world dose was critically important. Our dose of 40 IU/kg three times per week reflects the median from a recent analysis of the ATHNdataset (Croteau et al 2019), which reflects dosing among a large number of adult patients managed with standard half-life prophylaxis. Our model base case compares valoctocogene roxaparvovec to standard half-life FVIII products and not to Eloctate as was stated in the draft report summary. This dose does differ from dosing used in the ICER base case (80 IU/kg per week) and is at the upper end of the dose range for prophylaxis on the Advate label (20 to 40 IU/kg, 3 to 4 times per week). However, when patients elect treatment with gene therapy, they are able to forgo regular use of FVIII at doses that reflect real-world usage. The choice is not between valoctocogene roxaparvovec and FVIII prophylaxis dosed per clinical trials; rather, it is between valoctocogene roxaparvovec and real-world use of FVIII prophylaxis. Thus, we felt that real-world dosing for FVIII was the most appropriate model input.

We fully acknowledge that our choice to use the median wholesale acquisition cost (WAC) of standard half-life products means that costs in our model do not reflect the cost of a specific standard half-life product to any single payer. However, our model projects that valoctocogene roxaparvovec would be cost-saving on a lifetime basis as compared to standard half-life products even at the substantially lower per IU cost of $1.08 per IU used in the ICER base case analysis. Likewise, we chose to use a $2 million per patient average cost for valoctocogene roxaparvovec based on prices of currently marketed gene therapies in other therapeutic areas. However, our

model also projects that valoctocogene roxaparvovec would be cost-saving even at the $2.5 million price point used in the ICER draft analysis.

In summary, the main conclusion of this draft report is extremely sensitive to the assumed dosing of FVIII: in fact, it switches from valoctocogene roxaparvovec being highly not cost-effective to being dominant (and hence preferred). We do not see a good reason for not using real-world (vs. labelled) dosing.

Our inclusion of a 0.0004 disutility per infusion was an attempt to capture what some patients perceive as a burden associated with FVIII prophylaxis treatment. While the draft report background section describes FVIII prophylaxis as "burdensome" and notes the required intravenous access is "difficult to master and painful", there was no attempt to quantify the decrease in quality of life associated with frequent intravenous infusions or to include it in the cost-effectiveness model. Patients treated with valoctocogene roxaparvovec (and to a lesser extent with emicizumab) require a much smaller number of infusions over a lifetime, and the effect on quality of life is almost certainly non-zero. We did struggle to identify an appropriate value for the size of the disutility associated with infusions, and given the lack of hemophilia A-specific evidence, we used an estimate of injection disutility from another therapeutic area (Matza 2015). A more robust value for the input would be desirable, but we feel that including an imperfect estimate of the disutility associated with infusions was more appropriate than ignoring the impact of infusions on quality of life.

Now we would like to highlight two additional differences between our modeling approach and ICER's, which have significant impact on model outcomes. First, our model assumes that the cost of valoctocogene roxaparvovec will vary by patient weight. In particular, the heaviest patients will have a higher cost of valoctocogene roxaparvovec and also will have a higher cost of FVIII prophylaxis while the lighter patients will have a lower cost of both valoctocogene roxaparvovec and FVIII prophylaxis. In the ICER model, the cost of FVIII prophylaxis is linked to weight, while the costs of valoctocogene roxaparvovec is assumed to be $2.5 million per patient regardless of weight.

Second, in the draft ICER model, patients treated with valoctocogene roxaparvovec who experience a loss of response are assumed to initiate treatment with emicizumab. Our model instead assumes such patients would resume FVIII prophylaxis. Under our approach, the cost of treating patients in years after valoctocogene roxaparvovec loses effectiveness is identical to the cost of treating patients who never received valoctocogene roxaparvovec during those same years. Thus, our model is not very sensitive to variation in the model time horizon once the model horizon exceeds the typical duration of assumed valoctocogene roxaparvovec effectiveness. In the model presented in the draft report, however, the assumption of future treatment with emicizumab combined with the substantially higher treatment cost of emicizumab (compared to FVIII prophylaxis) means that model is very sensitive to time horizon. This finding is illustrated in the scenario in which patients receive valoctocogene roxaparvovec at age 40 instead of at age 18.

Thank you again for the opportunity to comment on this draft report. Please let us know if you have any questions about our comments.

Thank you,

Keziah Cook, Shaun P. Forbes, Kelly Adamski, Janice J. Ma, Anita Chawla, and Louis P. Garrison, authors of:

"Assessing the potential cost-effectiveness of a gene therapy for the treatment of hemophilia A", Journal of Medical Economics, DOI: 10.1080/13696998.2020.1721508

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September 22, 2020

RE: Bayer Response to ICER's Draft Evidence Report on the Assessment of Treatments for Hemophilia A

Dear Dr. Pearson,

Bayer Pharmaceuticals ("Bayer") appreciates the opportunity to comment on the Institute of Clinical and Economic Review's (ICER's) draft evidence report for the assessment of treatments for hemophilia A. Bayer is an enterprise with core competencies in the life sciences fields of healthcare and agriculture, with nearly 25,000 employees in 300 sites across the United States (US). Our products and services are designed to benefit people and improve their quality of life. At the same time, we aim to create value though innovation and are committed to the principles of sustainable development and to our social and ethical responsibilities as a corporate citizen.

Below are the key points that Bayer would like to emphasize in demonstrating that the ICER Evidence Rating of "B+" for emicizumab versus factor VIII prophylaxis should be lowered to "I":

1) There are concerns regarding the comparability of the HAVEN 3 and SPINART trials and the ability to draw conclusions from these trials with any level of certainty.
2) The heterogeneity of factor VIII products is not considered in the comparative clinical effectiveness assessment.
3) There are safety concerns of emicizumab that need to be further assessed and contribute to the uncertainty of the effectiveness of emicizumab compared to factor VIII prophylaxis.

Additionally, the dosing of factor VIII prophylaxis used in the scenario analysis is not representative of real-world dosing, and thus should not be used to make conclusions regarding cost-effectiveness.

The remainder of this letter provides a more detailed discussion of these points.

The ICER Evidence Rating of "B+" for emicizumab versus factor VIII prophylaxis should be lowered

Concerns regarding the comparison of HAVEN 3 and SPINART

The draft evidence report concluded with "high certainty that there is at least a small net benefit of emicizumab compared with factor VIII prophylaxis, and moderate certainty of a substantial net health benefit." As such, in patients with severe hemophilia A without inhibitors, the evidence for emicizumab compared with factor VIII prophylaxis was rated as "incremental or better" (B+; Rind 2020).

While it is unclear how much of the overall rating is based on the results of the network meta-analysis (NMA), as the report does not describe how the evidence considered was qualitatively or quantitatively synthesized to reach a net comparative rating, the evidence from the NMA likely contributed substantially to the overall rating. However, we believe the current rating greatly overstates the level of certainty of the comparative net health benefit of emicizumab that could have been obtained from the NMA.

The "ICER Evidence Rating Matrix: A User Guide" describes 5 major domains related to the strength of evidence that must be considered when determining the level of certainty: level of bias, applicability, consistency, directness, and precision (Ollendorf 2013).

1. Level of Bias: How much risk of bias is there in the study designs that comprise the entire evidence base?

There is substantial risk of bias due to differences in the 2 trials that were employed in the NMA (Rind 2020). First, the patient populations were substantially different in terms of age. In the HAVEN 3 trial, the median age was 40 years (range: 16-77; Mahlangu 2018). Conversely, the median age (incorrectly reported as 31 years in the ICER report; Rind 2020) in the SPINART trial was 29 years (range: 15-50; Manco-Johnson 2013; Manco-Johnson 2017). It is unclear if this difference may modify the treatment effects.

More problematic is the large discrepancy in the treatment duration between the 2 trials (24 weeks in HAVEN 3 vs 3 years in SPINART) included in the NMA (Rind 2020). While the ICER report concluded that "this was not expected to affect NMAs of bleeding rates, as these outcomes were annualized," the results from the SPINART trial do not support this conclusion. Results from the SPINART trial were reported with a treatment duration of 2 years (Manco-Johnson 2013) and then again with a treatment duration of 3 years (Manco-Johnson 2017). These results clearly show the annualized bleeding rates can change based on the treatment duration. For example, the mean treated bleeding rate per year in the on-demand treatment arm (no prophylaxis) changed from 30.5 at 2 years to 37.2 at 3 years (approximately a 22% change), and for the prophylaxis group, mean treated bleeding rate per year changed from 2.0 at 2 years to 2.5 at 3 years (a 25% change). Similar changes were also observed for the annualized treated joint bleeds.

The difference in the annualized bleed rate at 2 and 3 years within the SPINART trial also suggests that there were in fact differences in the baseline risk between the HAVEN 3 and SPINART trials. While the ICER report stated that the 2 trials had similar mean annualized bleed rates for the no prophylaxis arm (38.2 vs 37.2), this was based on a comparison of the annualized bleed rate at 24 weeks vs 3 years. When the comparison is made at 24 weeks vs 2 years, the baseline risk for annualized treated bleeds is 38.2 vs 30.5 (over a 25% difference). Given the clear impact of the treatment duration on the baseline risk for the annualized bleed rate, the difference at 24 weeks was likely even greater. The 2 trials did not report the bleed rates at baseline in a consistent manner that would lend itself to a clear comparison of the populations, so unfortunately, it is unclear if the difference in bleed rates existed at the outset. Ultimately, the bleed rate is highly likely to act as a treatment effect modifier for the 2 outcomes investigated. Given the differences in trial durations, combined with changes in bleed rates over time, it is likely that a substantial amount of bias exists in the NMA results.

2. Applicability: How generalizable are the results to real-world populations and conditions?

The trials both employed relatively small sample sizes (89 in HAVEN 3 and 84 in SPINART) and provided relatively little background information on the trial populations (Mahlangu 2018; Manco-Johnson 2013; Manco-Johnson 2018). Thus, it is unclear how representative these results are of the general population of individuals with severe hemophilia A without inhibitors, and consequently, the generalizability of the results is low to moderate, at best.

3. Consistency: Do the studies produce similar treatment effects, or do they conflict in some

ways?

As mentioned under the section on bias, the baseline risk in bleeding rates was likely different for the 2 trials. This has the potential to introduce heterogeneity and inconsistency into the NMA. Unfortunately, since there is only a single trial for each direct comparison, neither heterogeneity nor inconsistency could be quantitively assessed.

4. Directness: Are direct or indirect comparisons of therapies available, and/or are direct patient outcomes measured or only surrogate outcomes, and if surrogate outcomes only, how validated are these measures?

Only an indirect comparison of emicizumab vs factor VIII is available, with a single small trial for each treatment compared to no prophylaxis. While the results of the indirect comparison are highly questionable, the results within each trial clearly demonstrate that prophylaxis with either emicizumab or factor VIII is far superior to no prophylaxis in patients with severe hemophilia A. Further, both treatments appear to completely eliminate treated bleeding events for over half of the patients included in the trial (58% at 24 weeks for patients on emicizumab and 52% at 2 years for patients on factor VIII from SPINART; Mahlangu 2018; Manco-Johnson 2013). This result suggests that more clinically meaningful endpoint definitions beyond annualized bleed rate are needed to compare these treatments.

Another concern regarding the comparison of HAVEN3 and SPINART is the difference in comparator arms between trials. In SPINART, the comparator arm is on-demand treatment with Kogenate (Rind 2020); whereas, in HAVEN3, the “no prophylaxis” comparator arm does not describe which on-demand treatment is used (Mahlangu 2018).

5. Precision: Does the overall database include enough robust data to provide precise estimates of benefits and harms, or are estimates/confidence intervals quite broad?

There is a high level of uncertainty in both endpoints analyzed in the NMA. For annualized treated bleeds, the rate ratio 95% credible interval extends from 0.22 to 1.47, clearly spanning all 4 magnitude of effect categories (substantial net benefit to negative net benefit; Rind 2020). Similarly, for annualized treated joint bleeds, the rate ratio 95% credible interval extends from 0.2 to 1.39, again clearly spanning all 4 categories. Additionally, it should be noted that the exposure time in person-years (a very important data input for the NMA) was approximated for the SPINART trial, which introduces further uncertainty into these estimates.

Furthermore, results from the NMA showed a non-significant difference between emicizumab and factor VIII prophylaxis on bleeding outcomes of treated bleeds and treated joint bleeds (Rind 2020). Although the NMA results showed lower rates of treated bleeds and treated joint bleeds for emicizumab compared to factor VIII prophylaxis, the lack of a significant result on both clinical outcomes from the NMA indicate that there is no evidence to show that emicizumab has a greater clinical benefit than factor VIII prophylaxis.

Heterogeneity of factor VIII products

The heterogeneity of factor VIII products should also be considered in the assessment as data from SPINART may not be generalizable to all factor VIII products. Currently, a basket of over 15 factor VIII products have been studied and approved for prophylaxis. Additionally, Kogenate is a legacy standard half-life agent (studied from 2008 to 2011), and many newer agents have been approved since that allow for reduced treatment burden and have improved

pharmacokinetic parameters that reduce clearance and ensure higher exposure, as demonstrated in area under the curve (AUC) studies (Shah 2019).

Safety of emicizumab

All risk data for emicizumab should be considered. Although published clinical trial data for emicizumab from HAVEN3, HAVEN4, and HOHEMI reported no thrombotic adverse events or deaths (Rind 2020), long-term safety data is lacking. The median treatment duration from HAVEN3 is 29 weeks, from HAVEN4 is 25.6 weeks and from HOHOEMI is 39.1 and 32.1 weeks in the "3 mg/kg every 2 weeks cohort" and the "6 mg/kg every 4 weeks" cohort, respectively (Rind 2020; Shima 2019).

In the pooled HAVEN clinical trials, 3.5% of patients tested positive for anti-emicizumab antibodies and 1% of patients developed anti-emicizumab antibodies with neutralizing potential based on declining pharmacokinetics (HEMLIBRA 2020). One patient from HAVEN 2 developed an anti-emicizumab neutralizing antibody and experienced loss of efficacy after 5 weeks of treatment. Additionally, recent emicizumab data from clinical trials, expanded access, and compassionate use, showed 1 case of a serious thrombotic event from HAVEN 3, and recent emicizumab data from post-FDA approval showed 19 cases of thrombotic events in people treated with emicizumab, all of which were not in cases that met criteria for the boxed warning (excess on average of a cumulative amount of >100 U/kg/24 hours of activated prothrombin complex concentrate for ≥24 hours; Genentech 2020a). Unfortunately, the report on thrombotic events does not specify whether these events occurred in patients with or without inhibitors. In contrast, thrombotic events have not been reported in patients receiving factor VIII products such as Jivi (JIVI 2018). Recent emicizumab data from clinical trials, expanded access, compassionate use, and the postmarketing setting also showed deaths in 13 patients with congenital hemophilia A without factor VIII inhibitors, 3 patients with hemophilia A and whose inhibitor status was not reported, and 3 patients whose indication was not reported (Genentech 2020b). Taken together, there are safety concerns of emicizumab that need to be further assessed.

Summary

Therefore, when considering the 5 domains related to the strength of evidence (level of bias, applicability, consistency, directness, and precision), the heterogeneity of factor VIII products, and concerns regarding the safety of emicizumab, we believe the current evidence rating of "B+" overstates the level of certainty of the comparative net health benefit of emicizumab compared to factor VIII prophylaxis and suggest the evidence rating be revised to "I" to indicate insufficient evidence of a net health benefit.

The dosing of factor VIII prophylaxis used in the scenario analysis is not representative of real-world dosing, and thus should not be used to make conclusions regarding cost-effectiveness

In the ICER draft evidence report, scenario analyses were conducted using doses of factor VIII that were intended to be more representative of doses currently used in the US (Rind 2020). However, the doses of 118.2 IU/kg for Advate and 111.2 IU/kg for Eloctate were based on unpublished data that is not publicly available, and the methodology for how this data was collected is not described and therefore may be subject to bias and limitations. Specifically, the scenario analysis dosing represents a 48% increase from the base-case dose of 80 IU/kg for Advate and a 43% increase from 78 IU/kg for Eloctate.

While we appreciate ICER's willingness to incorporate real-world evidence into assessments, data used in the scenario analyses must be carefully selected and contextualized to ensure accuracy. An analysis of the Cost of Hemophilia: A Socioeconomic Survey (CHESS) dataset in the US using chart review and physician survey data demonstrated that extended half-life products have lower utilization compared to standard half-life products in the real-world setting. Patients receiving extended half-life products were found to use 9.0 IU/kg per week less than their standard half-life counterparts (mean of 70.2 IU/kg and 79.2 IU/kg, respectively; Curtis 2019).

Additionally, based on an internal claims analysis of real-world specialty pharmacy data from Symphony Health from July 1, 2018 to June 20, 2019 (among patients with hemophilia A, ≥6 fills, aged ≥12 years, with weight data available), real-world dosing of extended half-life products (Jivi, Eloctate and Adynovate) was consistent with the label midpoint (real-world dosing ranged from 97%-101% of label midpoint; Bayer 2020). Conversely, the real-world dosing of the standard half-life product (Advate) was 139% higher than the label midpoint (Bayer 2020). These data confirm that newer extended half-life products demonstrate narrow dosing ranges in the real-world setting that are consistent with the label dosing which allows for more predictability in utilization.

These studies show that there is variability in real-world factor utilization due to differences in study methodologies. While it is not clear how data provided by the American Thrombosis and Hemostasis Networks (ATHN) was collected, it is likely based on information from clinicians. Results from the CHESS US study, which was based on data collected from physicians, showed notably different utilization rates for both extended half-life (CHESS US: 70.2 IU/kg, ATHN: 111.2 IU/kg) and standard half-life (CHESS US: 79.2 IU/kg, ATHN: 118.2 IU/kg) products. While chart review data provide important information around what the physician ordered, claims data more accurately represent patient utilization and therefore are more appropriate to use for a cost-effectiveness model. Results from the specialty pharmacy claims data also showed notably different utilization rates from the ATHN data for extended half-life products (SP: 71.5-90.7 IU/kg, ATHN: 111.2 IU/kg). Given the large impact that factor VIII utilization can have on report conclusions, data used in the scenario analyses should be carefully selected, with consideration of the data source and methodology.

Lastly, the base case results showed that emicizumab had an incremental cost-effectiveness ratio of $10,393,000 per QALY relative to factor VIII, and the probabilistic sensitivity analysis results showed that emicizumab was found to be cost-effective at thresholds from $50,000 to $250,000 per QALY in only 14.0-14.5% of the simulations, which included scenarios with higher factor utilization. These results should be emphasized more in the conclusions on long-term cost-effectiveness to provide the reader with a complete picture of the long-terms costs of emicizumab compared to factor VIII prophylaxis.

We appreciate the opportunity to provide comments for this assessment and feel that consideration should be given to the points we have made to ensure a scientifically sound assessment.

Sincerely,

Todd Williamson, MSc
Vice President, Data Generation & Observational Studies,
Bayer HealthCare Pharmaceuticals Inc.

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September 21, 2020

Steven D. Pearson, MD, MSc
President
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Re: Comments on "Valoctocogene Roxaparvovec and Emicizumab for Hemophilia A: Effectiveness and Value – Draft Evidence Report", dated August 26, 2020

Dear Dr. Pearson:

On behalf of BioMarin, I appreciate the opportunity to provide comments on the Institute for Clinical & Economic Review (ICER)'s Draft Evidence Report for the ongoing assessment "Valoctocogene Roxaparvovec and Emicizumab for Hemophilia A: Effectiveness and Value." Given the US Food & Drug Administration (FDA)'s issuance on August 19, 2020 of a "Complete Response Letter"[1] in response to BioMarin's biologics license application for valoctocogene roxaparvovec, BioMarin agrees with ICER's statement that the results in this report should be considered "highly preliminary".[2] Since valoctocogene roxaparvovec will not be available to patients in the near term and more clinical data will be available for future consideration of marketing approval by the FDA[1], it would be premature to conduct and publish clinical and cost-effectiveness review of valoctocogene roxaparvovec or use the current assessment for any recommendations at this time. However, we appreciate that ICER recognizes the potentially transformative nature of valoctocogene roxaparvovec for hemophilia A and uses it as the first gene therapy to be reviewed under ICER's newly created Single and Short-Term Transformative Therapy (SST) framework. While any subsequent analyses would be based on a more comprehensive database, BioMarin would like to take this opportunity to comment on several aspects of the current draft report.

Under clinical effectiveness review, ICER rates the evidence as "promising but inconclusive" (P/I) comparing valoctocogene roxaparvovec to FVIII prophylaxis (FVIII) and the evidence as 'insufficient' (I) comparing valoctocogene roxaparvovec to emicizumab.[3] In cost-effectiveness review, ICER concludes valoctocogene roxaparvovec is not cost effective compared to FVIII in the base case. However, ICER also notes the results are highly sensitive to assumptions made in the model (e.g., valoctocogene roxaparvovec had >43% chance of being cost-effective in probabilistic sensitivity analyses at all listed willingness to pay thresholds). ICER highlights that the model drivers in the valoctocogene roxaparvovec model are costs of emicizumab and costs of prophylactic FVIII, parameters that are not related to the efficacy or cost of valoctocogene roxaparvovec. More importantly, the analysis shows that when doses of prophylactic FVIII reflecting current practice in the US are used, the model results are completely reversed, with valoctocogene roxaparvovec dominating prophylactic FVIII.

BioMarin's comments on ICER's Draft Evidence Report focus on three key aspects of ICER's approach to model development. We recommend that ICER includes additional evidence that

would improve current modeling methodology and potential relevance of findings for the US health system, specifically for three key components of the cost-effectiveness model:

(1) Treatment sequence and comparator
(2) Real-world doses and costs of FVIII replacement therapy
(3) Better capture of patient-relevant benefit beyond bleeds

(1) The cost-effectiveness model is inconsistent in assuming that follow-on long-term prophylaxis after valoctocogene roxaparvovec loss of efficacy will be with emicizumab rather than FVIII, while the comparator arm continues with life-long FVIII prophylaxis; such an approach is incongruent with appropriate economic assessment generally as well as the objectives and scope of this particular review.[4]

The draft model assumes that after treatment with valoctocogene roxaparvovec, once a patient's FVIII activity level dropped below 5 IU/dL (after 16 cycles or 8 years) and below 1 IU/dL (after 25 cycles or 12.5 years), 5% and the remaining 95%, respectively, of patients in the valoctocogene roxaparvovec cohort would switch back to prophylactic therapy. The model assumes that the prophylactic therapy patients would switch to is emicizumab, and all patients would remain on emicizumab for the remainder of their life.[a] Given the lifetime horizon of the model, patients will spend more time on subsequent therapy, which then drives the results, and the model becomes a comparison between emicizumab and FVIII. The decision to use emicizumab as the follow-on therapy alongside the reference scenario of life-long FVIII prophylaxis generates a comparison that is difficult to interpret and of limited applicability for decision makers, as the results are largely driven by the costs of emicizumab vs. FVIII, rather than the costs or the benefits of valoctocogene roxaparvovec.

BioMarin recommendations for ICER's updated model and future evaluation of hemophilia A:

- To minimize confounding of the analysis results by choice of follow-on treatment, the model should assume that if a patient switches back to continuous prophylactic therapy following valoctocogene roxaparvovec loss of efficacy, this would be to the same prophylactic treatment as in the comparator arm of analysis (i.e., if the comparator is FVIII, the follow-on treatment should be FVIII; and if the comparator is emicizumab, the follow-on treatment should be emicizumab).
- In future models, to better reflect the clinical reality, ICER could consider valoctocogene roxaparvovec follow-on therapy to be a mix of prophylactic therapies representing the market basket. In the comparator arm, treatment switches due to non-adherence issues should also be incorporated in the model.

[a] Of note, the analysis was inconsistent in the intended vs. actual choice of follow-on prophylactic treatment after valoctocogene roxaparvovec. Among the key model assumptions *[Draft Evidence Report p 47]*, the switch to prophylactic treatment at projected factor levels below 1 IU/dL would be to FVIII, unless emicizumab was the 'dominant' treatment in the parallel emicizumab vs. prophylactic FVIII cost-effectiveness model. Emicizumab was not cost effective vs FVIII in that model, and yet it was still used as the follow-on treatment in the comparison of valoctocogene roxaparvovec vs. prophylactic FVIII.

(2) The analysis would be most useful and relevant to the stakeholders when the doses and costs of prophylactic FVIII modelled reflect current clinical practice.

For the base case analysis, prophylactic FVIII doses used in the model were based on clinical trials (Advate for standard half-life treatment: 80 IU/kg/week; Eloctate for extended half-life [EHL] treatment: 78 IU/kg/week). However, the report also acknowledges that real-world dosing is often 40–50% higher than those used in clinical trials (Advate: 118.2 IU/kg/week; Eloctate: 111.2 IU/kg/week, based on recent market data from the American Thrombosis and Hemostasis Networks [ATHN]).[5] More importantly, ICER's own summary concludes that the cost-effectiveness results were completely reversed when the model incorporated FVIII doses that are more representative of current use in the US, with valoctocogene roxaparvovec dominating prophylactic FVIII.[6]

The SPINART trial from which the Advate dose was based is a global trial completed over a decade ago and does not reflect the current practices in the US as observed in the ATHN data set. Although there are limited efficacy data at these real-world doses, observations from the non-interventional study[7] conducted prior to the HAVEN 3 emicizumab trial and a recent analysis[8] of EHL products indicate that continued bleeding events occur at real world doses, including doses similar to those observed in the ATHNdataset.

In addition, the analysis used a one-time Wholesale Acquisition Cost (WAC) price of $2.5M as a placeholder price for valoctocogene roxaparvovec. However, for FVIII therapies and emicizumab, ICER attempted to estimate net revenue to the manufacturer of current chronic therapies based on Centers for Medicare & Medicaid Services (CMS) published Average Sales Price (ASP) limits, by removing the furnishing fees as well as add-on administration costs. By doing so, the analysis grossly underestimates the true health system impact of these therapies. Beyond Medicare, most people with Hemophilia A are covered under commercial payers who may cover hemophilia therapies under either the medical or pharmacy benefit; reimbursement is more likely to be based on WAC than ASP, and will include additional administrative costs (e.g., furnishing fee) as well.

BioMarin recommendations for ICER's updated model and future evaluation of hemophilia A:

- To reflect true health system impact and make the report more actionable, BioMarin requests that ICER models "real-world" FVIII usage with potential improved efficacy in the base case, and presents the clinical trial-based FVIII usage in scenario analysis.
- In addition, BioMarin requests ICER to use WAC for all therapies in this review to be better aligned with the costing methodology under ICER's value framework and make comparisons across a level playing field.[9]

(3) The cost-effectiveness model is an over-simplification of the clinical course and does not adequately capture the impact of disease and treatment on patients and families.

In the current model, patient health-related quality of life (HRQoL)/utility was tied only to discrete bleeding events and surgery. Despite the report acknowledging the substantial burden and adherence issues associated with chronic prophylactic therapies, the analysis did not factor in the

impact to patients of novel treatments with respect to reduced treatment burden and improved bleeding. ICER acknowledges that only 50–70% of patients with severe hemophilia A are adherent to prophylactic FVIII regimens due to substantial treatment burden[10], and valoctocogene roxaparvovec could provide patients with many years of treatment freedom and eliminate the adherence issue entirely. Patients could benefit from such freedom following treatment with gene therapy, which could provide profound patient benefits in terms of career/education choices, recreational activities, anxiety/depression, and overall well-being. While phase 3 data are not yet mature, patients treated with valoctocogene roxaparvovec demonstrated an increase from baseline in total scores—above and beyond the defined clinically important difference of 5.5 points—in the Haemophilia-specific Quality of Life Questionnaire for Adults[11] (Haemo-QoL-A) throughout 4 years in the phase 1/2 clinical trial.[12,13] Increase in score is mainly driven by changes in physical function, role function, worry and consequences of bleeding domains, and these results substantiate the broader patient benefits associated with one-time administration with valoctocogene roxaparvovec.

The analysis also fails to differentiate across worsening joint health states by assuming that the same utility value applies to all Petterson Score (PS) health states. PS is not a patient-relevant endpoint and is not a sensitive proxy for joint health morbidity. ICER considered joint health as a binary outcome (i.e., YES=PS 1–27, or NO=PS 0). This crude assumption fails to differentiate across worsening joint health states by assuming that the same utility value applies to all PS health states, substantially underestimate the benefits of slowing joint health morbidity, which is a bias in favor of treatments with worse bleeding outcomes.

BioMarin recommendations for ICER's updated model and future evaluation of hemophilia A:

- The model should incorporate a disutility associated with the frequent and burdensome infusions required for prophylaxis with FVIII of -0.0004 per infusion. [14]
- The model should differentiate utility values across PS health states to reflect progressive impact of accumulating bleeds on patient HRQoL.[15,16,17]
- More broadly, ICER should include the HRQoL benefit associated with a one-time treatment in ongoing SST value framework adaption. This would be a compelling opportunity for collaboration with stakeholders to develop novel methods and guide future evidence generation in this important area.

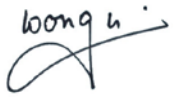
Finally, BioMarin cautions ICER to be aware of inherent assumptions made when mapping FVIII activity levels achieved with valoctocogene roxaparvovec to annualized bleeding rates (ABRs) seen in other studies of FVIII prophylaxis in order to attribute ABRs with gene therapy. Some investigators for valoctocogene roxaparvovec have suggested that the hemostatic efficacy of endogenously produced FVIII following gene therapy may differ from what might be expected in patients with mild or moderate hemophilia A, which are associated with mutations. While ongoing clinical trials will provide additional data to answer this question more definitively, we recommend that ICER consider mapping FVIII and ABRs or use the actual ABRs from valoctocogene roxaparvovec clinical trials in any future reviews.

Despite progress made in the standard of care for severe hemophilia A, many patients continue to experience breakthrough bleeds and the intensity of prophylactic regimen can have a major impact on their quality of life. BioMarin is committed to leading the way to the first ever gene therapy in

hemophilia A, and is confident that valoctocogene roxaparvovec has the potential to redefine the treatment paradigm.

BioMarin appreciates the opportunity to provide input on these preliminary findings of ICER's draft assessment on the comparative effectiveness and value of valoctocogene roxaparvovec and looks forward to providing additional data for inclusion in a future assessment closer to anticipated market entry. Please contact me with questions or clarifications.

Sincerely,



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As a person with severe hemophilia who has survived to celebrate my 76th birthday on October 10, 2020, I can reflect on the advances in treatment over the past seven decades. I have seen improvements in not only the safety and efficacy of treatments, clotting factors in particular, but also in issues of cost, storage, size, ease of administration, and length of effectiveness. I have confidence that my great-grandchildren if they have hemophilia, will benefit from miraculous treatment advances and perhaps even a cure. But each improvement carries with its choices and risks.

My recommendation is that research continues to make improvements in all these areas. The likelihood is that such improvements will be incremental and that patients and their hemophilia treatment centers should be free to choose among the many products that are and will become available. I urge that they should be given access to and the options to make their choices and the opportunity to choose their risks. Phase IV studies should be mandated where appropriate.

On December 21, 1991, I made a presentation to the FDA's Blood Products Advisory Committee, which was then considering the approval of the first recombinant produced clotting factor. I was told that some physicians had urged that the FDA license should deny the license because of alleged potential risks of inhibitor development. In response to those fears, I made the following presentation. Almost 30 years later, my advice is still applicable, and I repeat it in full here.

I want to introduce myself. My name is Donald S. Goldman. I am a person with hemophilia, the father of two daughters, both of whom are carriers. I am also a former president and chairman of The National Hemophilia Foundation. I was also a member of the National AIDS Commission. I am also a lawyer, practicing law in New Jersey. But I am speaking here not on behalf of any organization. I am speaking here on behalf of myself.

The first time that I received any blood products was a pint of whole blood before the Korean War. Afterward, I periodically received plasma and then fresh frozen plasma. Each such transfusion carried the risk of strange sensations, sometimes a sting, or a metallic taste in my mouth, and frequently, either moderate or severe hives, and the risk of hepatitis as well. I was lucky. Although physicians tell me that an intense, long-lasting flu when I was eight or nine was probably hepatitis, I never jaundiced and never developed chronic liver disease.

But each transfusion was a decision and a risk that my physician and I, or my parents, when I was younger, had to evaluate. A different set of choices and a different set of risks.

When I wanted to try out for Little League and had to choose between the risk of injury and the risk of taking clotting factor, I faced a different set of choices and a different set of risks. When I started using cryoprecipitate — sometimes, ten bags at a time — another set of risks appeared. Sometimes the units were tinged green, almost fluorescent, a result of the donor taking birth control pills, I was told. Another set of choices, another set of risks.

I remember some of the initial attempts to lyophilize cryoprecipitate. We used to call some of those attempts "bubble gum," which related to the consistency of the product that

resulted. And I remember that some physicians ridiculed efforts to purify clotting factor further, comparing such measures to the Pepsodent toothpaste commercial, as "trying to get the yellow out." Another set of choices, another set of risks.

I remember when NHLBI had a conference in the 1970s, entitled "Unsolved Problems in Hemophilia." My physicians reported that there were possible risks of long-term effects of cryoprecipitate or clotting-factor usage in terms of permanent liver or kidney disease. Another set of choices, another set of risks.

I remember the World Federation of Hemophilia meeting in New York in the mid-1970s and the views of some international experts that source-paid plasma was unsafe. Another set of choices, another set of risks.

And I remember very well in 1982 and 1983 when AIDS first reared its ugly head. Some physicians said that blood products did not even transmit AIDS; others said that AIDS was no more of a problem than hepatitis had been, and still others were more fearful. Questions of clotting factor versus cryoprecipitate were ever-present.

I recently re-read a letter that I wrote to my physician back in January of 1983, in which I discussed the dilemma of choosing between clotting factor, where source-plasma donors were asked about high risk behaviors, and voluntary single-unit cryoprecipitate, where donors were not so asked, because at that time the voluntary sector would not do such asking. That letter reflected the dilemma of which product to choose. Another set of choices, another set of risks.

I remember, in 1983 and 1984, when heat-treated products first appeared. Some physicians suggested that heat treatment might alter the molecule and cause inhibitors. Some argued that the increased cost did not justify their use. Some delayed switching to heat-treated products well into 1985 and some of those results may have been tragic. Another set of choices, another set of risks.

I remember the next few years when there seemed to be as many types of heat treatment as there were varieties of Heinz, different temperatures, different stabilizers, different periods. Another set of choices, another set of risks.

I can remember a few years ago when we had a shortage problem and I only had two bottles of clotting factor. It was a Wednesday night of a Thanksgiving weekend and I felt the beginning of a bleed in the knee. I had to decide whether or not I should use one of my two bottles that were left when I still had four or five days of the weekend ahead of me. Another set of choices, another set of risks.

I remember when solvent-detergent and monoclonal products appeared on the scene, seeming to be better choices. But I also remember learning of seroconversions in Germany and being reminded of the risk of manufacturing errors and Red Cross SNAFUs. I remember that for almost 50 years those of us with hemophilia have been the veritable canaries in the mineshaft in terms of our nation's blood supply. I remember that our courts have held that so long as they are derived from human blood, such products are unavoidably unsafe. Another set of choices, another set of risks.

I do not know what choice I would make if a recombinant product were available, and whether or not I would use it, but, if at all possible, I want my physician to have all the options so that we can choose the risks. I do not know if my daughters will have sons with hemophilia, but I want my grandchildren to have the options. I have spent the last 20 years trying to teach my children what I have learned about hemophilia and what I have learned about AIDS and what I have learned about life in general. I have tried to teach them to maximize their options, to make their choices and choose their risks. I do not urge that anyone use one type of product or another, but I do urge that they be given access to and the options to make those choices and the opportunity to take those risks.

That presentation was almost a quarter-century ago. When I learned about this FDA program, I re-read my 1991 statement and thought about how relevant it still was. Hence my being here today.

Let me bring you up-to-date. Less than a year after I spoke at the FDA, I was appointed as a Superior Court Judge, where I sat for the next 17 years. I continued to use clotting factor, bled into joints with regularity, but was able to continue to work fulltime. I had two knee replacements and enjoyed presiding over substantial criminal and civil trials. I retired in 2009 at the age of 65 to spend more time with my four grandchildren and join my wife, who had retired a few years earlier.

It turns out that while I was able to escape infection with HIV in the 1970s and 1980s, I did not escape hepatitis C. In 2010, a course of Interferon and Ribavirin left me with no benefit and lots of side effects. My viral load increased during treatment. Gradually my liver continued to deteriorate to the point of cirrhosis, and I became quite ill in 2011, 2012, and 2013. I was hospitalized and, when home, had little or no energy and stamina. Then in early 2014, new drugs became available, and my hepatologist suggested an off-label combination. Insurers rarely cover off-label usage, particularly for an expensive drug combination costing about $2,000 per day. Still, they agreed to cover it, and within ten days of treatment, my viral load became undetectable with no side effects from treatment. Unfortunately, relapses were reported in persons with cirrhosis who had been null responders on prior treatment, so my doctor wanted to continue the medication for another 12 weeks. I am not sure what I would have done if the insurers had denied the addition $150,000 in cost, but they approved it, so no hard choice was presented. Had it not been authorized, it would have meant another set of choices and another set of risks.

Thus, as you can see, the cost is an essential aspect of the balance between choices and risks. Having an effective treatment is of no importance if it is not affordable. When I went to Cuba in 2011, I met a young man who could hardly walk and desperately needed a knee replacement but cannot afford the necessary clotting factor to cover the surgery. For him, another set of choices and another set of risks.

And so, I conclude with the message that there will always be choices and risks in treating a complex chronic medical condition like hemophilia. The decision as to which choices to make and which risks to take is highly individualized and requires careful consideration by

collaborative discussions between patients, their families, and HTCs. There is no single answer. There is no one choice. There is no uniform risk.

Genentech
A Member of the Roche Group

September 23, 2020

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

Dear ICER Review Panel,

Genentech, a member of the Roche Group, appreciates the opportunity to provide comments on the *Valoctocogene Roxaparvovec and Emicizumab for Hemophilia A: Effectiveness and Value* Draft Evidence Report [1].

Hemlibra® (emicizumab-kxwh) is indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients ages newborn and older with hemophilia A (congenital factor VIII [FVIII] deficiency) with or without FVIII inhibitors [2]. As the first new class of medicine in nearly 20 years for persons with hemophilia A (PwHA), Hemlibra brought meaningful clinical change to a complex and heterogeneous disease with a significant unmet need [3-5]. Further, Hemlibra has been shown to be cost-effective in multiple peer-reviewed publications, for all PwHA (with and without FVIII inhibitors) [6-8].

To more accurately reflect current treatment patterns and enhance the clarity of the report, we make the following recommendations:

1) **Use the real-world FVIII dosing in the base case, as it represents current clinical practice and clinical guidelines.**
2) **Describe the methods and results of each model separately to avoid an inappropriate comparison of results across models.**
3) **Include an in depth discussion of the therapeutic benefits that are important to PwHA within the clinical and economic evaluation.**
4) **Increase transparency by adding the ability to modify the shared Excel model.**

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

1) Use the real-world FVIII dosing in the base case, as it represents current clinical practice and clinical guidelines.

Recommendations: The scenario analysis using real-world FVIII dosing should become the base case or be presented as a co-base case. The efficacy should be estimated based on target FVIII levels, which is consistent with the approach used for valoctocogene roxaparvovec. Specifically, assume FVIII levels at >3-5% to be consistent with clinical guidelines [9], and apply the corresponding annualized bleed rate from den Uijl et al [10].

Rationale: The base case FVIII dosing referenced from the SPINART trial [11] is not consistent with real-world dosing, the Advate prescribing information, and clinical guidelines [9,12-14]. Therefore, the real-world dose provided by the *American Thrombosis and Hemostasis Network* of 118.2 IU/kg for Advate and 111.2 IU/kg for Eloctate should be used [1]. Doing so aligns with *The World Federation of Hemophilia* Guidelines that recommend prophylactic treatment targeting higher FVIII trough levels (>3-5%+) [9].

Implications: The current base case substantially underestimates FVIII utilization and consequently, incorrectly lowers the total cost of therapy, thus overestimating the cost-effectiveness profile of FVIII prophylaxis [1,15]. Given the large discrepancy between the scenario and base case analyses, there appears to be high uncertainty in the results, bringing into question the validity of ICER's base case analysis. Using the real-world dose of FVIII is aligned with standard US clinical practice and allows healthcare decision makers to appropriately interpret the value of therapy.

2) Describe the methods and results of each model separately to avoid an inappropriate comparison of results across models.

Recommendations: (1) The methods and results for the valoctocogene roxaparvovec adult model (Model 1) and the Hemlibra child model (Model 2) should be presented as separate sections in the report. (2) Distinct tables and figures, with footnotes denoting each model as an independent analysis, should be added to the report.

Rationale: The current report presents all figures, tables, and text for both models jointly, which invites comparisons that should not be made. Moreover, three different frameworks are deployed in conducting the assessments with unique underlying context. In attempting to fit these distinct models into one report, aspects of the review are misconstrued. For example, the model structure (Figure 5.1) incorrectly depicts the populations entering the models at the same Pettersson Score, when in fact they are different [1].

Implications: By presenting the model results side-by-side, readers may erroneously interpret the results as being from the same model, and miss the important differences such as levels of underlying evidence and the patient populations. Readers also may make incorrect cost-effectiveness comparisons between Hemlibra and valoctocogene roxaparvovec, when no such comparison exists. Broadly speaking, stakeholders with a lay knowledge of cost-effectiveness, such as the press, may make comparisons that are not valid and can lead to unintended consequences with regard to patients' access to therapy.

3) Include an in depth discussion of the therapeutic benefits that are important to PwHA within the clinical and economic evaluation.

Recommendations: ICER should more thoroughly discuss the benefits of the interventions on lifestyle and life decisions, patient preferences, and FVIII inhibitor development. In addition, the Report-at-a-Glance and Executive Summary should also contain this information.

Rationale: Section 2.2 describes restrictions of hemophilia such as career flexibility, education choices, physical activity, family structure, and geographic mobility. ICER's previous 2018 hemophilia A review highlighted the positive impact of less frequently dosed therapies on these restrictions [16]. However, the potential impact of therapy on these concerns is not addressed in the current clinical or economic evaluations. In a rare disease with a high patient burden, an intervention's potential benefits and contextual considerations on patient-relevant outcomes such as patient preferences and quality of life should be emphasized [17,18].

An additional important patient-relevant outcome is Hemlibra's potential to delay inhibitors. As we previously noted, FVIII inhibitor development has historically been an unpredictable and burdensome treatment complication. A sizable portion of PwHA (~30%) [9,19] will develop inhibitors and this population will face higher costs [20]. There is strong clinical rationale for Hemlibra delaying FVIII inhibitor development. This outcome is linked to FVIII exposure, which is lowered in PwHA treated with Hemlibra [7,21]. Published economic models have accounted for the risk of FVIII inhibitor development [7,8] and should be leveraged and weaved into the overall discussion in this report.

Furthermore, one of the *Comparative Effectiveness Public Advisory Council* voting questions focuses specifically on "Potential Other Benefits and Contextual Considerations". By expanding the discussion of patient-relevant intervention impacts, the voting members will be better prepared for a robust discussion.

Implications: Incorporating these important considerations and outcomes will increase the relevance of this assessment, particularly to PwHA. Notably, including these considerations would improve the face validity of the analyses by addressing well-documented concerns and key complication of the disease.

4) Increase transparency by ability to modify the shared Excel model.

Recommendation: The *Model Transparency Program* should allow users to modify model inputs, and run scenario and sensitivity analyses.

Rationale: The intended purpose of model sharing is to facilitate feedback on the draft report. The modeling good research practices from the *International Society for Pharmaceutical Outcomes and Research* recommend a model is transparent and can be validated to increase confidence [22]. This is achieved by allowing relevant parties to review a model's structure, equations, parameter values, and assumptions. However, many of the parameter values in the model (e.g., therapy switch probabilities) are locked, and screen protections in critical trace and calculations tabs prevent formula auditing and important pressure testing of alternate inputs (e.g., time-dependent efficacy). This presents challenges in running critical scenarios that assess the accuracy and validity of the model (i.e., sensitivity and scenario analyses cannot be replicated). Manufacturers, like Genentech, can and have provided accuracy checks that ensure end tools are error-free and clinically valid.

Implications: A model with the ability to run scenario and sensitivity analyses will enable stakeholders to better understand and quality check the analysis, strengthening confidence in the results.

Genentech
A Member of the Roche Group

Conclusion

We are confident in the value of Hemlibra based on the comprehensive clinical evidence supporting its sustained safety and efficacy, and importantly the real-world and cost-effectiveness evidence to date [6-8,23-28]. Taking into account the issues that PwHA have identified as life altering, Hemlibra represents a significant innovation in the hemophilia A landscape. Genentech is dedicated to partnering across the healthcare system to ensure all patients have access to the medicines they need. Our recommendations will enhance the accuracy of ICER's assessment and relevance of the report. We welcome the opportunity to discuss these recommendations further.

Sincerely,

Jan Elias Hansen

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Genentech
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September 23, 2020

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

Re: Draft Evidence Report ICER's Review of Valoctocogene Roxaparvovec and Emicizumab for the Treatment of Hemophilia A

To Whom It May Concern,

I am writing to you on behalf of the European Haemophilia Consortium (EHC), a European non-profit organisation that represents 47 National Member Organisations (NMOs) of people with rare bleeding disorders such as haemophilia and von Willebrand Disease. The EHC aims to provide assistance to countries in order to access the safest and most efficacious treatments in a timely and cost-effective manner. As a result, we are aware, of initiatives such as those initiated by the Institute for Clinical and Economic Review (ICER). Recognizing the importance of this work, we are providing input that can allow a better understanding of the available options. ICER's 2018 report on the sub-population of people with haemophilia (PWH) with inhibitors provided a very pragmatic approach to cost effectiveness modelling when there was little available evidence. In bridging the evidence gap, ICER included studies that were ultimately more relevant to current clinical practice, resulting in a model that ultimately added significantly to the understanding of the cost effectiveness and benefits for PWH with inhibitors.

We commend ICER on creating the opportunity for patient organisations to provide feedback on this report before it is finalized.

Report Readability
In the report, having two models in single tables in section 5 may create some misunderstanding of the comparisons, especially as the FVIII prophylaxis models are different. Model 1 and 2 deal with slightly different cohorts, so direct comparisons are not possible. At first glance, a reader may misinterpret which model is the base case. For clarity, it would be better to split the tables dependent on the model used for each drug and base case. Alternatively, if the tables are to remain together, it would be preferable to have a single FVIII base case, rather than two separate FVIII base cases, which is confusing for the reader.

Additionally, in the PICOTS, there was an indirect comparison mentioned in terms of evidence for Emicizumab and Valoctocogene Roxaparvovec, but this has not been described in the model. It would be interesting to report this in the results section, or alternatively, removed from the early section. The former option would be beneficial in understanding the differences in benefits for each type of treatment.

Patient Relevant Data
In the clinical trials of both treatments being assessed, Haem-A-QoL, a disease specific quality of life measure for haemophilia, was recorded and has been reported. While utility scores are beneficial in our community's understanding of the impact of such treatments, it would give greater context to the discussion if ICER were to consider reporting disease specific outcomes.

In the 2019 ISTH HAVEN study abstract[1], data demonstrates that the proportion of participants with no missed workdays increased to ≥90% with Emicizumab prophylaxis in both HAVEN 3 and HAVEN 4[1]. This may be a result of patients having extended periods without bleeding, and it could be included in the model under societal costs for Emicizumab, and may potentially be considered in those patients in the Valoctocogene Roxaparvovec model. If this is not possible, further expansion of the descriptive analysis should be provided.

In terms of patient relative data, there are two areas that we would like to see reported. The first is frequency of infusion. There is a cohort of patients with needle phobia and poor venous access, which can have implications on adherence. The number of infusions required for a life-time of prophylaxis significantly impacts patients' quality of life[2]. It should be possible to report these from the model and give a better indication of the number of infusions that are avoided; whether they be subcutaneous or intravenous infusions, this is still several hundreds of infusions avoided in either case.

The second request is to consider using a pharmacokinetic model for the FVIII dosing, and report the time over a life-time that a patient spends above 10-12%. The rationale for this request is based on Den Uijl et. al. work, demonstrating the significantly reduced likelihood of bleeding above this level[3]. Signs of this are also seen in the ISTH HAVEN study abstract[1].

The combination of both of these would allow fairer comparisons when considering how changing to these treatments, or even remaining on a patient's current treatment, might impact their individual quality of life for the future. If possible, these might be considered by ICER when reviewing this draft.

FVIII Utilization

In 2018, ICER correctly identified that the data available on the inhibitor population was severely lacking, and took a pragmatic approach in assessing the current literature on treatment. As a result, ICER produced a model that mimicked the care available to patients in the clinic extremely effectively. In this case, there was just enough evidence defined in the literature review to qualify for a comparison of clinical trials versus randomized control trials such as SPINART. In this report, as a result, the discrepancy between modelled FVIII utilization and the real-world evidence provided by ATHN is significantly different. On this occasion, the lack of assessment of what is currently happening in clinics all over North America and Europe is totally different than the SPINART comparison. Historically, troughs of 1-3% were being targeted in these trials. In the EU and US, with patients having access to extended half-life or standard half-life products at higher doses, this paradigm is shifting significantly. The European Directorate for the Quality Medicines and Healthcare (EDQM) has stated that minimum trough levels of 3-5% be targeted in order to provide protection from joint damage[4]. EDQM recommendations are recognised guidelines endorsed by the Council of Europe.

A pharmacokinetic (PK) based model would better demonstrate the reality of current FVIII use in clinics and would provide FVIII utilisation closer to that seen in the ATHN dataset. Additionally, this would make the 'scenario' analysis more applicable. Across health sectors, there is an increasing recognition of the importance of personalized medicine. We hope ICER would use the same pragmatic thinking demonstrated in the past, and use more recent publication of FVIII utilization and trough levels, to inform the model.

Additionally, reporting the real-world analysis, identified through the ATHN dataset on pages 70-71, is one of the most interesting aspects of the report. As a reader, until this point is reached in the report, the message transmitted is that these products are highly un-cost-effective; then in this small section, it is suddenly highlighted that if real world evidence from ATHN is used, they do become cost effective. ICER's model, while not a pharmacokinetic one, is well structured. However, the huge difference between real

world and model outputs makes it difficult to believe that the model is a true representation of what might happen if these products are made available. The model could be used in many countries as a reason for not introducing a cost-effective therapy, while in reality ICER identifies that they could be significantly cost-saving. Addressing the FVIII usage in both Model 1 and Model 2 would add validity to outputs on FVIII utilization. We recommend that, at the very least, this section is expanded and an additional scenario analysis be reported, identifying the new probability of these products being cost effective.

Inhibitor Development

The draft report indicates that de-novo inhibitor development was not considered. While we appreciate that ICER made this decision in order to simplify the model, this omission does not reflect real-world conditions. Additional information on possible implications of this decision should be added to the descriptive analysis for the reader; such an analysis should comment specifically on avoiding the development of FVIII inhibitors in the short-term in previously untreated patients (PUPs), balanced with the lack of data available on what might happen from a patient's perspective regarding delayed inhibitors due to lack of exposure to factor replacement.

Biological Activity of Post Gene Therapy FVIII

The draft report notes that "The manufacturer of Valoctocogene Roxaparvovec has suggested that the low bleeding rate seen even as factor VIII levels decline imply that the factor VIII produced by gene therapy may be more biologically active than the factor VIII in patients with mild or moderate haemophilia." Such speculative statements are often reported, but do not actually have any basis or add benefit to the report. We would recommend removing this section from the report.

Durability

This is a topic of significant debate currently, especially for FVIII gene therapies. In these models, it also has a significant impact on the interpretation of whether the treatment is cost effective or not. We suggest firstly that data is reported using the chromogenic assay. Secondly, if possible, we recommend that an analysis of duration be carried out and used to inform considerations towards a 'fairer price' for gene therapy. The main rationales for this is to prevent another redrafting of this report in the future, to help guide potential cost savings, and to further inform the types of payment models that would be recommended.

Thank you, once again, for allowing comments at the draft stage. We hope that the suggestions highlighted above may be beneficial to ICER's model, US health systems, and many other countries in the world who look to ICER for guidance on cost effectiveness. If you have any additional questions or need further clarification, please do not hesitate to contact us.

Yours sincerely,

D Noone

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Declan Noone
President, European Haemophilia Consoritum

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September 23, 2020

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

RE: Draft Evidence Report on the Assessment of Treatments for Hemophilia A

Dear Dr. Pearson,

This letter is written in response to the recent Institute for Clinical and Economic Review (ICER) draft evidence report on the assessment of treatments for hemophilia A on behalf of the International Hemophilia Access Strategy Council (IHASC), a multi-stakeholder group of health economists, physicians, patients, and health technology assessment (HTA) experts. As part of this council, the HTA considerations subgroup seeks to raise awareness of the particular aspects of gene therapy in hemophilia and the performance of assessments that account for the multi-dimensional value of these treatments. While this initiative is supported by Bayer, the company does not control the ideas or intellectual content coming out of the group.

We share the common goal of helping to ensure that evidence-based, innovative therapies for hemophilia can reach the patients that need them. Given the opportunity to review the ICER draft evidence report, we hope to provide a useful contribution to the upcoming review of the first gene therapy in hemophilia A.

We respectfully offer three key recommendations regarding the draft evidence report for hemophilia A:

1. Given variability in dosing and associated outcomes across factor VIII prophylaxis products in clinical trials and real-world studies, assumptions from both data sources need to be carefully considered due to its impact on cost-effectiveness outcomes.
2. Given the lack of patient-relevant benefits currently incorporated into utility values, ICER should integrate these patient-relevant factors into the baseline and post-interventional utilities of their cost-effectiveness models.
3. We respectfully suggest that the results of this report and its implications on the value of a gene therapy treatment option in Hemophilia A not be taken as definitive due to gaps in evidence.

Below is a more detailed discussion of these points.

Given variability in dosing and associated outcomes across factor VIII prophylaxis products in clinical trials and real-world studies, assumptions from both data sources need to be carefully considered due to its impact on cost-effectiveness outcomes.

The estimation of factor utilization used for the cost-effectiveness analysis is critical. Because the model is highly sensitive to assumptions on utilization, we suggest ICER provides further detail about utilization based on varying ranges to better understand thresholds of cost offsets.

Differences between dosing of factor VIII prophylaxis and associated patient-relevant outcomes in clinical trials and that in the real world may be pivotal to cost-effectiveness findings regarding any treatment vs factor VIII prophylaxis. Regarding clinical trial utilization, there is a detachment that is not accounted for in the method of integrating utilization into the base case

cost effectiveness model. Although there is a rationale for utilizing SPINART as the clinical trial to represent factor VIII products from an efficacy perspective, there are multiple classes of factor VIII products and using just one trial cannot accurately represent all approved factor VIII products, nor their treatment regimens, nor the outcome levels achieved. Additionally, we support the use of real-world evidence in the ICER draft evidence report; however, these real-world utilization rates should be supported by sound evidence and should also be accounted for by their effects on outcomes. In the report, the evidence is limited to only one real-world study without detail of the method in which it was captured, and thus enables the selected sample to influence the conclusion of the report completely.

As such, we recommend that ICER identify and use data from multiple credible sources of data including clinical trials and studies using real-world evidence to represent factor product utilization and efficacy/effectiveness. This will ensure that treatments across multiple classes of factor VIII products are represented and that one study or treatment is not unfairly weighted in the analysis.

Given the lack of patient-relevant benefits currently incorporated into utility values, ICER should integrate these patient-relevant factors into the baseline and post-interventional utilities of their cost-effectiveness models.

The goal of increased utilization is to target higher trough levels which results in substantial patient benefits, including reduced bleeds and improved outcomes over time (Lambert 2018; Peyvandi 2019; Jimenez-Yuste 2014). However, the cost-effectiveness model in the assessment does not comprehensively capture the additional patient benefits. The model limits any potential improvements that may arise strictly to productivity and reduced bleeds but does not account for the importance of improving the clinical phenotype and does not acknowledge the decreased disease burden associated with an improved phenotype or sustained protection.

A patient-centered outcomes framework for assessing value in hemophilia has been created and includes 3 tiers: 1) health status achieved or retained, 2) process of recovery, and 3) sustainability of health. Within each tier, there are several metrics that should be considered when assessing the value of hemophilia treatments (O'Mahony 2018). Currently, there are factors important to value assessment from all three tiers that the cost-effectiveness model does not incorporate, such as function/activity, pain, and health-related quality of life (physical, mental, emotional, and social functioning). The current model structure with its utility values strictly based on bleeds and Pettersson scores misses these key components that would enable a multidimensional integration of patient benefit.

We respectfully suggest that the results of this report and its implications on the value of a gene therapy treatment option in Hemophilia A not be taken as definitive due to gaps in evidence.

We understand ICER's limitations regarding available evidence when conducting this assessment which was further substantiated by the FDA's decision to ask for longer term efficacy data for valoctogene roxaparvovec.

However, to better inform future assessments and account for the distinct profiles of each incoming gene therapy, we want to highlight the need for manufacturers to generate the evidence establishing comparative data of an intervention versus the standard of care and to disseminate

this information prior to submission to health authorities and payers for reimbursement when possible.

For future reports on SSTs, it may also be beneficial (in situations where the price and durability of a product is unknown) to develop scenarios of testing varying duration of effect or alternative prices that may inform discussions around alternative payment models between manufacturers and payers.

We very much appreciate this opportunity to provide public input on the draft evidence report of the assessment of treatments for hemophilia A. We hope that our contribution will help to inform future transparent, evidence-based assessments.

Sincerely,

IHASC HTA Considerations Subgroup

Clifford Goodman and Bengt Jönsson

(With comments provided by Peter Neumann)

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September 22, 2020

Institute for Clinical and Economic Review
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Boston, MA 02109

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

To Whom It May Concern:

Thank you for the opportunity to provide comments to the Institute for Clinical and Economic Review (ICER) on the Draft Evidence Report reviewing Valoctocogene Roxaparvovec (BioMarin Pharmaceutical, Inc.) and Emicizumab (Genentech, Inc) for the treatment of people with hemophilia A (PwHA) without inhibitors compared to Factor VIII (FVIII) replacement therapy. We are pleased to submit the following comments elaborating and expanding upon our prior submissions.

The National Hemophilia Foundation (NHF) and Hemophilia Federation of America (HFA) are national non-profit organizations that represent individuals with bleeding disorders across the United States. Our missions are to ensure that individuals affected by hemophilia and other inherited bleeding disorders have timely access to quality medical care, therapies, and services, regardless of financial circumstances or place of residence. Both organizations accomplish this through advocacy, education, and research.

Our organizations are also dedicated to finding better treatments and cures for inheritable bleeding disorders. People living with hemophilia have long dreamt of the day when they would see a cure or a transformative therapy that would dramatically reduce their burden of disease and allow a quality of life similar to those not affected. As NHF and HFA assess new therapies and interventions, we are ever mindful of these yearnings and will closely evaluate whether the novel treatments will meet our community's goals and expectations.

Report Organization

Although described in the original PICOTS, ICER did not complete a comparison of Emicizumab directly to Valoctocogene Roxaparvovec. The fact this analysis was not completed should be clearly indicated.

Combining the results of the two completed model versions (FVIII v Emicizumab, FVIII v Valoctocogene Roxaparvovec) in one blended discussion leads to confusion and potential misinterpretation. This presentation is potentially misleading and risks readers concluding the tables are intended to provide a direct comparison between Emicizumab and Valoctocogene Roxaparvovec. For example, tables such as 5.10 summarizing the results of the base case analysis present results which are derived from significantly different inputs (e.g., age, starting Pettersson score, bleed rates, dosing). The data presented for total costs, reduced joint bleeds, life-years gained and QALYs are not comparable.There is no mention of the differences in inputs when Table 5.10 appears in the report. A reader would need to recall or refer 15 pages earlier to find a description. For clarity we request the report be split between the two models.

Patient Relevant Outcome Data Not Acknowledged

In ICER's 2018 report reviewing clinical effectiveness and value of Emicizumab for PwHA with inhibitors to FVIII, ICER commented, "In assessing the value of treatments for hemophilia, payers should be aware of important benefits and contextual considerations that are not typically captured in cost-effectiveness analyses." As patient organizations,

we have spent an enormous amount of time thinking about and generating high-quality Health Related Quality of Life (HRQoL) data that measures outcomes important to patients. Traditional methods of cost effectiveness analysis struggle to capture the potential for broader benefits to patients and society. This difficulty is even more apparent when considering transformative or curative therapies. Where data (direct or indirect) is available, we request that it be fully characterized within the ICER report.

For this review, we submitted data to ICER demonstrating patient benefit for several key metrics. We are disappointed that ICER did not analyze all the available direct qualitative evidence and indirect evidence reporting on core patient outcomes.

Specific to Emicizumab, the report incorrectly states that ICER did not identify any studies assessing the impact of prophylaxis with Emicizumab on "Other Outcomes." This statement may lead readers to miss or downgrade key information regarding Emicizumab's demonstrated and clinically significant beneficial impact on patient-relevant outcomes.

The Haem-A-QoL instrument used in the Haven 3 and 4 studies is currently the most widely used hemophilia-specific instrument for the evaluation of HRQoL in PwHA. Haem-A-Qol provides a composite score of many outcomes important to patients (physical health, feeling, view of oneself, sports and leisure, work and school, treatment, future, family planning, partnership and sexuality) as well as individual domain scores. The physical health domain is an important facet of the Haem-A-QoL that measures the high impact of hemophilia A on physical activity. Use of this instrument is a recognized strength of the HAVEN studies. The improvement seen in the physical health sub-score for patients treated with Emicizumab demonstrated clinically relevant differences between Emicizumab and FVIII prophylaxis.

It is also our understanding that the sponsor provided ICER with data expanding on a 2019 ISTH HAVEN study abstract (Ref 38), in anticipation of a forthcoming manuscript. The additional data demonstrate that the proportion of participants with no missed workdays increased to ≥90% with Emicizumab prophylaxis in both HAVEN 3 and HAVEN 4. (Ref 38) We request the report reflect the observations of this patient-relevant metric.

The frequency of infusions required for prophylaxis regimes significantly impacts PwHA quality of life.[1] We request ICER consider accounting for treatment burden in the model.

Relative to gene therapy, real-world comparative data on the use of Valoctocogene Roxaparvovec is not available from clinical trial data. However, the PROBE study (referenced in our earlier submissions) provides relevant indirect evidence demonstrating a difference in outcomes for PwHA by phenotype. While PROBE does not collect head-to-head data for comparison of specific drugs, submitted data responded directly to elements within the ICER Data Request (bleed disutility, impact on joint range of motion, arthropathy, utility values) for PwHA with severe disease, PwHA with severe disease on prophylaxis, and PwHA with a mild phenotype. Additional data were in-press (now published) reporting on other comorbidities, acute and chronic pain, pain occurrence and interference, pain medication frequency, impact on activities of daily living and use of mobility aids by phenotype.[2] PROBE validation was described in prior submissions.

The data presented provide important contextual information for the ICER analysis and modeling to establish baselines, as well as indicate potential anticipated outcomes if individuals were to achieve a milder phenotype. It is unknown if someone born with a mild phenotype is equivalent to someone who attains a mild state through gene therapy. Nevertheless, data indicate that the phenotypic disease state does matter, not just in terms of clinical outcomes, but also for patient-important outcomes directly impacting quality of life. While some PwHA living with a milder phenotype still encounter significant negative impacts from their hemophilia, data demonstrate overall improvement across the metrics for those living with mild disease or no hemophilia. The ICER report should include a descriptive analysis clearly reflecting the value of living with a less severe phenotype.

FVIII Dose Selection Not Based on Real-World Utilization

We are likewise troubled that ICER did not adopt utilization data that is based on real-world experience. The goal of any cost effectiveness model should be to reflect as closely as possible real-world scenarios, so that the resulting

analysis is credible. There are statements within the report (e.g., "we are uncertain of the added efficacy of these higher doses"; "especially at currently used dosages") which appear to call into question more contemporary factor utilization. If these statements remain in the final report, we ask that you indicate that such statements are outside the scope of this review and the analysis should in no way be used to assess current standards for optimal dosing strategies for factor replacement prophylaxis. There is significant clinical consensus that microbleeding, breakthrough bleeding, and other negative sequelae often result when standard prophylaxis targeted to a 1% trough level is utilized. Such suboptimal treatment does not meet WFH Guidelines, which state that "Dosing and dosing intervals should be sufficient to prevent spontaneous and breakthrough bleeding and hemarthrosis." (Ref 25) Indeed, WFH treatment guidelines recommend escalation of prophylactic doses as necessary to achieve these goals.

A model built on a pharmacokinetic (PK) analysis could accommodate a real-world outcomes-based approach for utilization. Across health sectors, there is an increasing recognition of the importance of personalized medicine. Within the field of hemophilia this is often achieved through PK-guided dosing. In the absence of utilizing PK based data, it is difficult to comprehend why the base case model is not built on contemporary representative data from the real-world derived directly from the national registry (ATHN dataset).

Rather, the base case inappropriately relies on utilization data from the SPINART study (Ref 45, 46). The SPINART study was undertaken in response to an unmet need for data to establish the benefits of secondary and tertiary prophylaxis in adult PwHA, in high-resource and low-resource countries, who had at least 150 exposure days to any factor product and who had established arthropathy. To be in the study, a PwHA had to have anywhere from 6-24 bleeding episodes in the 6 months prior to enrollment and not be on prophylaxis. This is a group that essentially does not exist anymore in the United States.

SPINART was a significant research study at the time. Hematologists have learned from research such as SPINART and adjusted clinical practice accordingly, precisely as we expect from a learning health care system. The older model of therapy studied in SPINART would not be considered standard of care for a PwHA receiving care through a federally supported Hemophilia Treatment Center today. The study data is now over a decade old (data collected between 2008 and 2013). It is no longer generalizable to the standard of care in 2020.

Additionally, SPINART was conducted prior to the first US approval of an extended half-life FVIII product (Eloctate 2014). It also preceded foundational research such as that conducted by den Uijl et al (Ref 53) which provided critical insight into the importance of FVIII levels relative to joint bleeds. The den Uijl work, along with the introduction of extended half-life products, have significantly contributed to substantial changes in treatment practice in the years since the SPINART study was conducted and published. For many PwHA, higher trough levels and thus higher utilization are required to prevent joint bleeding. Even at the time, the dosing utilized in SPINART (25 IU/kg) was considered suboptimal for many PwHA.

ICER should not build its base case analysis around data which is outdated and unrepresentative of current clinical practice. To do so disregards the objectives of hemophilia treatment today (e.g., normalizing quality of life, preserving joint function, and eliminating bleeding). We request ICER recognize the fundamental flaw in the base model assumptions and replace the utilization data of the base case with the real-world data provided by ATHN.

Moreover, we are concerned that ICER's relegation of the real-world analysis to page 70-71 of the report could be interpreted as devaluing the therapeutic advances of recent years that have led to better outcomes for PwHA. The report fails to capture the clinical gains achieved with higher factor utilization. The comments on page 70-71 summarizing the model variations based on real-world (rather than outdated) data should be prominently moved to the beginning of the report and fully highlighted in the Executive Summary.

NHF and HFA share ICER's concern over the availability of real-world evidence and robust patient-relevant outcomes data across the lifecycle of drug development. We appreciate that there are challenges in using real-world data for economic evaluations; however, where such (systematically collected) data exists, ICER should recognize and utilize it. We are hopeful this review serves as a framework and reminder to all stakeholders that the generation of clinically- and patient-relevant outcome data should remain a high priority early in clinical development, and that the timely presentation of patient-relevant data matters for economic evaluations conducted by ICER.

Uncertainties and Controversies

Inhibitor Development (page 39)

The draft report's models omit any consideration of inhibitor development, the most significant treatment-related event today for severe PwHA. While we appreciate that ICER made this decision in order to simplify the model, this omission does not reflect real-world conditions. There is no way to predict which PwHA will or will not develop an inhibitor. Readers need to understand the resulting cost analysis omits this important, highly costly and highly impactful adverse event. Assumptions substantially differing from the real-world must be explicitly stated in the table of assumptions (Table 5.1).

In addition, we request ICER consider a scenario analysis modeling inhibitor development for previously untreated patients beginning prophylaxis at birth with FVIII concentrates relative to an assumed rate for those who begin with Emicizumab or gene therapy. Such an analysis would be informative for both health systems and PwHA on the total burden of hemophilia.

Biological Activity of post gene therapy FVIII (page 40)

The draft report notes that "The manufacturer of valoctocogene roxaparvovec has suggested that the low bleeding rate seen even as factor VIII levels decline imply that the factor VIII produced by gene therapy may be more biologically active than the factor VIII in patients with mild or moderate hemophilia". This speculative statement has no basis in fact. It has not been peer-reviewed and the sponsor has submitted no evidence to support it as a hypothesis. Thus, please omit this speculative and unsupported statement.

We recognize the gene therapies being developed for PwHA today may be just the first step toward a curative therapy; however, along the way, we should not legitimize a notion that low factor activity expression measured by bleeding events alone is an acceptable outcome for gene therapy. Non-severe hemophilia is not benign. The metrics for differentiating gene therapy from standard of care extend beyond bleed rates.[3] In the absence of peer reviewed longitudinal data fully characterizing clinically- and patient-important outcomes including joint preservation, absence of sub-clinical joint bleeding (microhemorrhages) and impact on HRQoL from diminished factor activity levels, the inclusion of such post-hoc speculation risks uncertainty for both progress which has been made for the existing standard of care, but also the future evolution of treatment.

Durability

The durability of gene therapy is a critical component to defining successful gene therapy. It is also, of course, key to understanding the therapy's cost-effectiveness. NHF and HFA are ever mindful that a diagnosis of hemophilia imposes significant financial burdens on both PwHA and their families, as well as on the overall health system. We therefore share a common interest in seeking economic value for treatment, and are concerned when a medication's price misaligns with the value it provides. Clarity in the interplay of price and durability of a gene therapy will aid our understanding of the potential health care cost savings that could be obtained over a lifetime (or alternative period of durability) and the calculation of a "fair price".

ICER describes methods for estimating durability of factor activity (page 59) for both "an optimistic scenario (starting at a factor level of 89 IU/dL and using the proportional decline seen from year 3 to 4 to project) and a conservative scenario (same starting point as the base case and using a linear projection of decline)." The Cook model described on page 68 reports an average successful duration of gene therapy of roughly 11 years to 5% factor activity. It is difficult for readers to interpret and compare the various approaches modeled. Providing the duration required for cost-effectiveness at a given price (or, conversely the price for a gene therapy that would meet cost effectiveness for a known duration) would be highly insightful. Given this is a number derived from a population (e.g., mean, median), if median is used, half the patients will be below, and half above 5% and this should be taken into account in the prediction of durability. Analysis based on Factor VIII activity derived from chromogenic assays is recommended by the sponsor of Valoctocogene Roxaparvovec.[4] In the future, each gene therapy manufacturer will need to demonstrate which assay (one-stage or chromogenic) provides useful predictive information for comparison of the population

treated. We request ICER include a table reflecting the duration of effectiveness to 5% modeled by ICER for Valoctocogene Roxaparvovec in each of the analyses.

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 complete this review.

Sincerely,

Leonard A. Valentino, MD
President & Chief Executive Officer
National Hemophilia Foundation

Sharon Meyers, EdD, CFRE
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Institute for Clinical and Economic
Review 2 Liberty Square
Boston, MA 02109

September 22, 2020

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

Novo Nordisk appreciates the opportunity to participate in ICER's review of valoctocogene roxaparvovec and emicizumab for hemophilia A. Given the potential this report is used in decision-making, Novo Nordisk would like to comment on several topics from the report:

Comments

1. **Relying on the SPINART study to represent efficacy for all FVIII products does not acknowledge innovations over the past decade which have led to lower ABRs with FVIII products.**

Novo Nordisk's understands the logic that ICER used to identify the SPINART study for the NMA, however, the issue is that the SPINART study was conducted from 2008 to 2011 with a SHL FVIII dosed at 25IU/kg, 3x per week.[1] Over the past decade, hemophilia treaters have identified other dosing strategies to reduce ABRs and new EHL products have been improved with superior pharmacokinetics. Both have resulted in improvement in bleed protection which is not reflected in this ICER report. To highlight this point, Esperoct is the latest product to be available in the US which achieved an average ABR of 1.2[2] (slightly less than that seen with emicizumab in HAVEN 3) and well below the 4.56 ABR used for FVIII products in the modeled base case. Again, we understand why SPINART has been chosen, but we ask ICER acknowledges in the Uncertainty and Controversaries section of the Evidence Report that SPINART is older data and results may have been different if other sources of FVIII efficacy were used in this review.

2. **The Scenario Threshold Analysis where real-world dosing of FVIII products is compared to trial dosing of valoctocogene roxaparvovec and emicizumab is limited in its applicability in that it does not compare apples to apples.**

While real-world dosing is available for FVIII products, we do not yet know how emicizumab is dosed in the real world, and given the concerns about durability, it is unclear what the real world cost of care will be with valoctocogene roxaparvovec. Therefore, if ICER continues to keep the Scenario Threshold Analysis in the Evidence Report, it is suggested that ICER adds this point to the Limitations section of the Evidence Report.

Additionally, given higher real-world doses compared to clinical trials are being used in the Scenario Threshold Analysis, it is likely that the ABRs would be lower. While ICER, addresses this on page 77 by stating "We are uncertain of the added efficacy of these higher doses, but even if these doses completely eliminated all bleeding events (and thus had greater efficacy than emicizumab), emicizumab would remain cost effective." While that may be true, ICER could still use real-world bleed rates in the base case for this Scenario Threshold Analysis as it has implications for the conclusions made. Malec and colleagues (2020) analyze the ATHN dataset and find an average 1.3 ABR for all patients receiving

FVIII (1.0 and 1.9 for EHL and SHL, respectively).[3] Using these ABRs may likely change the conclusion on page 66 such that while valoctocogene roxaparvovec and emicizumab would still be projected to save costs, QALYs may not be higher in versions 1 and 2 of the model. Novo Nordisk asks that ICER include this in the model and update this conclusion.

3. **The Scenario Threshold Analysis utilizes dosing from ATHN (118.2 IU/kg every week for Advate and 111.2 IU/kg every week for Eloctate) which may not be representative of other FVIII products.**

ICER has used Advate and Eloctate as 'representative treatments of each type, and typical doses for those products' (page 53). While they may be the most prescribed SHL and EHL FVIII products, their labeled dosing regimens are anything but typical for each type of FVIII they represent in this report. Advate and Eloctate both have significant dosing flexibility as per the FDA label which may have contributed to the higher real-world doses derived from ATHN and may not be representative of other FVIII products.

Advate is recommended to be dosed at 20 to 40 IU/kg every other day (which is up to 140 IU/kg per week) or every third day with dosing targeted to maintain FVIII trough levels ≥ 1% (allowing for even higher weekly doses). Eloctate is recommended to be dosed in the range of 25-65 IU/kg at 3-5 day intervals (which is up to 152 IU/kg per week). Other EHL FVIII products have less flexibility and lower maximum dosing amounts per week [Adynovate: 40 to 50 IU/kg twice per week (up to 100 IU/kg per week); JIVI: 30 to 40 IU/kg twice per week (up to 80 IU/kg per week) or 50 to 60 IU/kg every 5 days (up to 84 IU/kg per week)] while others have simple, fixed recommended dosing (Esperoct: 50 IU/kg every 4 days = 87.5 IU/kg/week). Therefore, these FVIII products likely have lower weekly doses in the real world than what ICER has modeled in this scenario. In fact, a study was published earlier in 2020 found statistically significant differences in weekly dosing for EHL products.[4]

To address this issue, Novo Nordisk suggests that ICER publish the weekly doses for each of the FVIII products in the Evidence Report as captured within the ATHN database for readers to assess if the real-world dosing for Advate and Eloctate are indeed representative of other SHL and EHL FVIII products.

Novo Nordisk also suggests that ICER discusses the issues that are present when using Advate and Eloctate to represent all SHL and EHL products in either the Uncertainty and Controversaries or the Limitations section of the Evidence Report. Here, ICER could highlight differences in labeled dosing regimens which have an impact on the real-world dosing for each product. Furthermore, in the case of EHLs, ICER could state that the different methods used to extend half-life have had different levels of success when compared to SHL products (ranging from Adynovate's 40-50% half-life extension in adolescents and adults[5] to Esperoct's 85% half-life extension in children[6]) and pharmacokinetic differences between EHLs[7] which further explain labeled dosing differences.

Finally, given the implications of this scenario analysis, ICER would best serve readers of the Final Evidence Report by adding more information on how these dosing amounts were derived from the ATHN Dataset. Were FVIII dose and frequency provided by HTCs or patient dairies? Does it represent their prescription or actual product utilization? If it based on prescription, we suggest ICER states if 100% adherence to the prescription has been

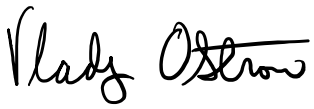
assumed. As ICER has noted throughout the report, adherence is a factor to consider with hemophilia treatment and Novo Nordisk advices that ICER adjust this real-world scenario for an appropriate adherence rate given this is being represented as real world dosing and cost. Furthermore, ICER could state if these doses are median or mean values. All of this information is important to provide context to the reader so that they can put these findings into context.

CONCLUSION

Novo Nordisk would like to thank ICER for their consideration of our response.

In summary, we suggest that ICER more clearly informs the reader of the Evidence Report that there are differences between FVIII products, specifically when it comes to EHLs, and using one product to represent all of them, has limitations. Given the approach to use representative products for SHL and EHL, we suggest that ICER rethink the use of blanket statements defining the value of all SHL and EHL products when only Advate and Eloctate were included in this model. At a minimum, ICER could note this in the Uncertainty and Controversaries or Limitation section of the Evidence Report.

We look forward to seeing our comments being addressed within the Final Evidence Report and appreciate the opportunity to provide feedback.



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7. Shah A, Solms A, Wiegmann S, et al. Direct comparison of two extended-half-life recombinant FVIII products: a randomized, crossover pharmacokinetic study in patients with severe hemophilia A. Ann Hematol 2019;98:2035-2044.

PATIENTS RISING NOW

September 23, 2020

Steven D. Pearson, MD, MSc, FRCP
President
Institute for Clinical and Economic Review
One State Street, Suite 1050
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RE: Draft Evidence Report "Valoctocogene Roxaparvovec and Emicizumab for Hemophilia A"

Dear Dr. Pearson:

Patients Rising Now advocates on behalf of patients with serious and chronic conditions and diseases for have access to life-improving and life-saving therapies and services. Access to such treatments and services is essential, and it spans affordability, insurance coverage and physical access. To support improved access, we are committed to engaging patients, caregivers, physicians, media, health policy experts, payers, providers and others to foster people-centered discussions about the entire U.S. health care system. Our goal is a balanced dialogue that illuminates the truth about health care innovations and advancements in a transparent and equitable way.

We appreciate the opportunity to provide our comments on ICER's August 26th Draft Evidence Report "Valoctocogene Roxaparvovec and Emicizumab for Hemophilia A." After some introductory observations, our comments about the draft report are organized below into the following sections: People-Centered Perspectives; Value Viewpoints about Cures for Serious Diseases; ICER's Budget Impact Assessment Process; and Additional Points.

We have previously submitted comments to ICER about emicizumab concerning its 2018 review about the use of that medicine for people with hemophilia A with inhibitors.[i] We would like to note that ICER's current draft report addresses the use of emicizumab for people with hemophilia A who do not have inhibitors, and that the trials of the gene therapy valoctocogene roxaparvovec were also conducted in people with hemophilia A without inhibitors.

The FDA approved emicizumab for use in people with hemophilia A without inhibitors on October 4, 2018.[ii] We point this out because we believe that in discussing the clinical situation for people with hemophilia A it should be made more explicitly clear that the current draft report: 1) Is addressing a different subset of patients with hemophilia A than ICER's 2018 report;[iii] 2) Is reviewing a second FDA-approved indication for emicizumab; and 3) People with hemophilia A develop inhibitors after receiving factor VIII. For example, the draft report notes that "the development of inhibitors has very important implications for management, costs, and quality of life."[iv] But simply referencing ICER's 2018 report here is inadequate. We strongly feel that the draft report should contain more extensive discussions of the differences between the two groups of people with hemophilia A, the natural course and history of how people with hemophilia develop inhibitors and what that means for their treatment and care options, costs,

and lives.[v] An updated and complete discussion of those matters is important not only for patients and clinicians to assess ICER's work, but also for policy makers and payers to be able to determine the utility of ICER's reporting for their internal health technology assessments and related practices and policies. In addition, to parallel ICER's 2018 report, we believe the report's title should include the phrase "without inhibitors," i.e., "Valoctocogene Roxaparvovec and Emicizumab for Hemophilia A Without Inhibitors."

People-Centered Perspectives

As noted above, the current draft report focuses on people with hemophilia A without inhibitors. From the perspective of people with hemophilia A – and their family and caregivers – the goal is to achieve as normal a life as possible, which the draft report reasonably presents by discussing the many challenges and life limitation people with hemophilia currently face.

We are again somewhat dismayed that ICER proceeded with examining valoctocogene roxaparvovec even after the FDA declined to advance its own review, which essentially pushes back the earliest approval date to late 2021 or sometime in 2022. Given that the remainder of the review concerns emicizumab, which was originally approved in November 2017,[vi] we fundamentally question the utility of the draft report: Is the purpose to review data about an approved indication that is now two years old, i.e., for hemophilia A without inhibitors? Or to review data that will be updated in about a year with additional information before any potential decision could be made by the FDA? Either of those scenarios has limited utility to patients, clinicians, payers or policy makers. Specifically, policy decisions about additional uses for emicizumab have already been established, and clinical decision makers should already be familiar with the information. Similarly, it is premature to make any clinical or policy decisions about valoctocogene roxaparvovec. Thus, the draft report's assessments and "findings" are inherently unactionable for those audiences.

Similarly, the report is not actionable for payers and policy makers, who work on an annual or biannual timeframe that corresponds to benefit plan years. For them, emicizumab's second approved indication should already be incorporated into their processes, and while valoctocogene roxaparvovec should be on their radar, it is not a factor they need to consider now. In fact, they cannot evaluate it until the additional research required by the FDA has been conducted and analyzed. ICER's review seems premature at best.

The draft report also minimizes the real patient implications of having to receive treatments or prophylaxis intravenously versus subcutaneously. This difference between emicizumab and factor VIII is important, particularly for people with hemophilia A who have transportation or mobility limitations or live in geographic areas where access to clinical facilities for intravenous treatments may require many hours of travel.

Those differences in route of administration can also make the real-life benefits and utility very different from what is reported in clinical studies, particularly as they may be calculated in a meta-analysis of multiple studies. We noted that the draft report includes the sentiments of patients that support this real-world benefit, "98% of patients favored emicizumab over factor VIII prophylaxis,"[vii] and "all caregivers [in the HOEHEMI trial] indicated the lower frequency of treatment and easier route of administration as the major reasons for their preference for emicizumab."[viii] And as the draft report states, "If reductions in adherence outside of trials are not

similar for the two therapies [clinical trial data] could incorrectly characterize the relative benefits of the therapies in the real world. Emicizumab prophylaxis is substantially less burdensome than factor VIII prophylaxis, and so real world adherence is likely to be more similar to clinical trial adherence with emicizumab than with factor VIII."[ix] Similarly, such real-world adherence differences could translate into great benefits for people, particularly because the draft report found that "Emicizumab appears to have lower bleeding rates (of all types) compared with factor VIII."[x] If ICER's goal is to affect real-life policies and actions rather than to provide guidance for future research studies, we urge ICER to expand its recognition and discussion of such people-centered factors.

Value Viewpoints about Cures for Serious Diseases

Because the draft report includes information about valoctocogene roxaparvovec as a potential gene therapy despite the FDA's decision to defer action, we believe it is appropriate to comment on the meaning of such treatments. While it seems from the currently available data that valoctocogene roxaparvovec may have some waning of effectiveness after several years, it also needs to be viewed through the lens of how medical progress actually occurs. Similar to how biplanes were not directly or immediately replaced by jets, improvements in treatments occurs incrementally – sometimes with small steps, and sometimes in larger leaps. Clearly the development of a gene therapy that is effective for several years is a leap over injections that must be given every few weeks. However, valoctocogene roxaparvovec should also not be viewed as the finish to the race for gene therapies. Indeed, improvements will be made upon that very large step, with the ultimate goal of having reliable, stable, and permanent cures. Thus, the initial leap – in this case valoctocogene roxaparvovec – needs to be viewed in its context as part of a process of treatment advancements. For example, in viewing the advancement that valoctocogene roxaparvovec potentially represents, the variability of individual responses to treatment as depicted in Figure 4.1 in the draft report is illuminating. Such individual variability indicates that there is much still to be learned about the use of such gene therapies, and how to customize or adjust their use for individual patients, which – again – is part of the process of innovation and the advancement of scientific knowledge to improve care and outcomes.

For patients, such significant leaps represent hope in concept – as well as in reality – that better treatments will be developed while they are benefiting from those that are small steps or significant leaps, but that still leave them with some impairment, limitation or dependence upon ongoing treatments. This value of hope is real for patients even if payers, policy makers, and quantitative modelers are unable or unwilling to incorporate that reality for patients into their cognition and conclusions. We hope that as ICER continues to refine its processes and practices it will be able to better include that value and similar perspectives of real patients.

ICER's Budget Impact Assessment Process

ICER correctly determined that because valoctocogene roxaparvovec is not yet approved and more research is ongoing, the draft report should not include a Budget Impact analysis for this potential gene therapy. We applaud this decision, as such hypothetical exercises can do more harm than good.

However, in the past we have expressed concern about certain technical and procedural components of ICER's Budget Impact analyses, and with the current draft report there is an additional confusing aspect. Specifically, the draft report includes a Budget Impact analysis for emicizumab, even though it is not a newly approved compound; FDA approved this medicine in

November 2017. We find this inconsistent with ICER's potential Budget Impact analysis formula that includes the number of newly approved medicines as a fundamental factor. This is problematic because to anyone familiar with the reality of the U.S. health care system, off-label uses of approved medicines is both common and an expected and necessary part of quality health care, except in very rare circumstances. Thus, ICER's conducting a Budget Impact analysis on a 3-year-old medicine presents a murky analytical rationale within ICER's theoretical Budget Impact evaluation process.

We would appreciate ICER clarifying how it will consistently conduct potential Budget Impact analyses based upon original versus subsequently approved indications. We eagerly await ICER's insights about how it can be more consistent and coherent in this particular facet of its activities.

In addition, as we discussed in our comments to ICER's 2018 draft report about the use of emicizumab,[xi] people with hemophilia are not evenly distributed among all the different payers in the U.S. Specifically, data indicates that people with hemophilia are much more likely to be insured by Medicaid, and less likely to be insured by Medicare or the Veterans Health Administration. (It is not unreasonable to postulate that they are also very unlikely to be covered by the Department of Defense's health system.) However, when a curative gene therapy for hemophilia is available, those differences may disappear. We are not advocating that ICER attempt to include such forward, evolutionary modeling into its work – since our impression is that ICER prefers to view the future as a static situation – but we believe it must be part of broader discussions concerning how budget impact should be conducted, and modeling of potential future scenarios could be constructed.

Lastly, we would be remiss if we did not point out that ICER's style of global budget impact assessments don't account for the patient perspective: what matters to patients and their families is their actual costs, not some aggregate for the entire country. And further, regarding health system or payor budgets and spending, people with serious and chronic conditions have intense concerns about how any budget or access restrictions will impair innovations that could help treat or cure their health problems, and improve or prolong their lives – real-world implication that are generally missing from ICER's work and activities.

As we've stated before, and continue to maintain, presenting a "budget impact" analysis for the health care spending across the entire United States is essentially a fictional story.

<u>Additional Points</u>

- We are confused by the lack of inclusion of Serious Adverse Events in the Long-Term Cost Effectiveness Model inputs[xii] since in ICER's 2018 report SAEs were included in the model at a rate of 3%.[xiii] If there is a difference in clinically observed SAEs in people with and without inhibitors then this certainly should be presented and discussed by ICER.
- ICER's SST framework that arbitrarily picks caps of $150,000/patient/year or 50% over a lifetime for the amount of "cost savings" that a company might receive from a new treatment in this category[xiv] continues to be puzzling. We are particularly concerned about treatments – such as gene therapies – that could be very expensive to produce and administer, and as such if either the $150,000 number or a 50% threshold of "cost savings" were somehow

implemented, it could result in net losses for the company, leading to the discontinuation of the treatment or service.

- Reference #13 should be updated to the link for the most current label for emicizumab since the text refers to both the initial approval for hemophilia with inhibitors and the subsequent approval for hemophilia without inhibitors.
- The year for the World Federation of Hemophilia Guidelines should be 2020 not 2012.[xv]
- There is reference in the text to an economic model in a 2017 ICER report,[xvi] but there is no citation or footnote.

Conclusions

Patients Rising Now is pleased that people with hemophilia A have access to different treatment options, and that other new and better treatments and cures appear to be on the horizon. However, we are concerned that access to current and future treatments may be limited or barred by insurance plans and their agents through formulary design, cost-sharing structures, or prior authorization requirements because of ICER's activities, which may at the same time expand administrative burdens for clinicians and patients.

Sincerely,

Terry Wilcox
Co-Founder & Executive Director, Patients Rising Now

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[i] http://icerwatch.org/wp-content/uploads/2018/10/02232018-Patients-Rising-Comments-to-ICER-RE-HemophiliaA-FINAL-1.pdf
[ii] https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-emicizumab-kxwh-hemophilia-or-without-factor-viii-inhibitors
[iii] https://icer-review.org/material/hemophilia-a-final-evidence-report/
[iv] Draft report, p. 39
[v] For example, from the CDC: https://www.cdc.gov/ncbddd/hemophilia/inhibitors.html; from the Hemophilia Federation of America: https://www.hemophiliafed.org/understanding-bleeding-disorders/complications/inhibitors/; and from UpToDate: https://www.uptodate.com/contents/inhibitors-in-hemophilia-mechanisms-prevalence-diagnosis-and-eradication
[vi] https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-emicizumab-kxwh-prevention-and-reduction-bleeding-patients-hemophilia-factor-viii
[vii] Draft report, p. 28
[viii] Draft report, p. 29
[ix] Draft report, p 39
[x] Draft report p. 42
[xi] http://icerwatch.org/wp-content/uploads/2018/10/02232018-Patients-Rising-Comments-to-ICER-RE-HemophiliaA-FINAL-1.pdf
[xii] Draft report, p. 52
[xiii] "Emicizumab for Hemophilia A with Inhibitors: Effectiveness and Value" Final Evidence Report, April 16, 2018, p. 45, Table 4.8
[xiv] Draft report, p. 58
[xv] Draft report, p. 17 and reference #25
[xvi] Draft report, p. 67

PIPC Partnership to Improve Patient Care

September 23, 2020

Dr. Steven D. Pearson
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Dear Dr. Pearson,

The Partnership to Improve Patient Care (PIPC) appreciates this opportunity to comment on the Institute for Clinical and Economic Review's (ICER) draft evidence report regarding treatments for Hemophilia A. PIPC has repeatedly made the point that ICER conducts its assessments too early, often prior to FDA approval and before adequate data is available to conduct a robust and fair assessment. In this particular assessment, one of the drugs being reviewed was recently denied approval by the FDA due to uncertainty of evidence. Given the extreme change in timeline for this drug's approval and future availability, this assessment should have been halted. In addition to our concerns about this assessment being incredibly premature, we would like to highlight several other areas of the assessment.

ICER neglects to use available real-world data

In most cases, using real world data on healthcare utilization as an alternative to data from a clinical trial has a very strong justification and will be more reliable. This has been outlined quite clearly by ISPOR[1] and many other leading experts in the field of health economics.[2] Populations in clinical trials tend to be on average much healthier than those in the real world, as many grounds for exclusion from clinical trials such as existing co-morbidities, age, ongoing current treatment failure can mean exclusion at registration and other factors can lead to withdrawal from the trial once it begins[3]. Additionally, individuals participating in clinical trial settings tend to receive a much more intensive form of healthcare regime due to study requirements and close monitoring of patients, ultimately resulting in better overall control of the studied disease. This can also result in a reduction in acute or adverse events associated with their respective condition that would not otherwise be replicated outside of the trial setting.

ICER's draft evidence report relies on RCT data for its base case but also contains a discussion that indicates both therapies are cost saving when "real world usage" of Factor VIII is

[1] Garrison Jr LP, Neumann PJ, Erickson P, Marshall D, Mullins CD. Using real-world data for coverage and payment decisions: The ISPOR real-world data task force report. Value in health. 2007 Sep;10(5):326-35.

[2] Pearl J. Generalizing experimental findings. Journal of Causal Inference. 2015 Sep 1;3(2):259-66.

[3] Stuart EA, Bradshaw CP, Leaf PJ. Assessing the generalizability of randomized trial results to target populations. Prevention Science. 2015 Apr 1;16(3):475-85.

incorporated into the model rather the use measured from RCT populations. It is our opinion that the real-world data source for use of Factor VIII should be used in the base case. If this had been done, ICER's results could look very different with more reflective utility inputs, incorporating mortality effects, better long-run data on effectiveness and assuming Factor VIII costs that are more reflective of the real world.

ICER's use of the quality-adjusted life year is inappropriate

As we have noted in many previous comment letters, the use of the quality-adjusted life year (QALY) in ICER's evaluations is inappropriate and discriminatory, as it is inherently biased against people with disabilities and patients suffering from chronic illnesses, like hemophilia.

The use of the QALY in this assessment is particularly concerning given the health state utility valuations (HSUV) used. It is widely acknowledged that people experiencing chronic illnesses and disabilities regularly adapt to their conditions. This leads to what is known as disease state adaptation or hedonic adaptation—when patients and people with disabilities to overestimate their own quality of life. The result of this is that assessments relying on these HSUVs will undervalue treatments being assessed. Hedonic adaptation is a well-documented phenomenon among hemophilia patients. In fact, a paper written by some of the same authors as the paper from which ICER sources its utility values puts this point forward and makes clear that it should be considered when conducting economic evaluations for hemophilia.[4]

ICER omits outcomes that matter to patients

Organizations representing patients with hemophilia expressed to ICER early in the review process that, although annualized bleed rates are important, there are other factors that matter deeply to patients, including chronic pain and mental health. ICER neglected to incorporate these patient-reported outcomes in its model, and we encourage ICER to do so prior to the release of the final report. Furthermore, the National Hemophilia Foundation and Hemophilia Foundation of America requested in their previous letter that ICER include Factor Activity Level, Chronic Pain, and Mental Health in its assessment outcomes. They noted that, " Where data are not available for the outcomes of interest (those listed in the Draft Scoping Document and the additional outcomes noted above) or a metric is not yet established, ICER should nevertheless recognize the full set of outcomes within its valuation as they are of importance to patients. Such recognition will guide future clinical trials and the planned real-world evaluations noted in the 2020-2023 ICER Value Assessment Framework." We agree with and echo this request. It is seminally important that value assessments move in the direction of capturing data on outcomes that actually matter to the ultimate user, the patient. As a leader in the HTA field, it is ICER's responsibility to move assessments in a direction rooted in patient-centeredness and accounts for their feedback.

[4] Martin A, Mulhern B, Shaikh A, Asghar S, O'Hara J, Pedra G, Sawyer EK, Li N. Disease State Adaptation Experienced By Patients with Hemophilia: Literature Review and Expert Consensus.

ICER makes the questionable assumption of no mortality effects

ICER noted that it expects no mortality effects to result from treatment with either therapy.

Specifically, ICER implied that as prophylaxis for hemophilia A in patients without inhibitors has not been demonstrated to decrease mortality, then there should be no mortality effect as a result of the treatments being studied. This is an oversimplification and appears to contradict other studies. The same paper[5] ICER references to make this justification suggests that the 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 remove 12 years from 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 was despite the fact that those with hemophilia were 57% less likely to die from ischemic heart disease than controls.[6] There is also evidence of reduced inhibitors in those treated with emicizumab, which is a known risk factor for morbidity. Even though findings were mixed in smaller studies due to their role in mortality, recent larger studies also suggest that they are an important factor and can increase risk of death by up to 70%.[7] Additionally, a similar study concluded mortality rates were five times higher in Hemophilia A patients with inhibitors, than those without.[8]

By assuming no mortality effects from treatments deemed to be highly effective in treating a disease known to have higher rates of premature death, ICER is underestimating the true "value" of these therapies.

ICER oversimplifies health states

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Transition probabilities between Pettersson score (PS) health states are based on expected annual joint bleed rates and a literature-based assumption that on average 36.52 joint bleeds result in an increase of the PS by 1 for patients under 25 and 6.52 joint bleeds result in the same shift for patients aged 25 years or more.

There is a significant difference between these rates, and the use of only these two buckets oversimplifies the patient experience. The result of this oversimplification may be to over- or under- estimate the true value of therapies dependent on the age at which the treatment starts. As such, it would make far more sense to use a regression model to determine the relationship between number of joint bleeds and PS score, than it would to have just two categories covering a wide level of heterogeneity across patients.

Conclusion

ICER should seriously reconsider moving forward with this assessment, given the fact that one of the drugs has recently been denied FDA approval. If ICER does insist on pushing forward with the assessment, we urge the organization to take into account our above comments in order to ensure a more robust and accurate assessment that reflects the lived experiences of patients with hemophilia.

Sincerely,

Tony Coelho
Chairman
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20 September 2020

Submitted via Email

Email: publiccomments@icer-review.org

My dear Dr Pearson

PUBLIC COMMENT: DRAFT EVIDENCE REPORT

VALOCTOCOGENE ROXAPAVOVEC AND EMICIZUMAB FOR HEMOPHILIA A

Thank you for this valuable opportunity to comment on the Draft Evidence Report for Valoctocogene Roxapavovec and Emicizumab in hemophilia A [1].

You are, I know, aware of my concerns that the ICER reference case framework for value assessment fails to meet the standards of normal science. 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. 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 is why I have coined the term impossible or I-QALY as you and many others insist in believing that ordinal utilities have multiplicative properties [2].

This, possibly harsh, conclusion rests on the failure to recognize, and you and ICER are not alone, the limitations imposed by the axioms of fundamental measurement. You focus on constructing simulated QALY claims yet we know that the utility score (typically the EQ-5D-3L/5L) is an ordinal measure [3]. It cannot support multiplication which is required to transform modelled time spent in a disease state to

its quality adjusted time equivalent. This means the QALY is a mathematically impossible construct. I am not asking you to agree, but if you want to create a QALY then the utility scale must have ratio properties. The EQ-5D scales do not. Apart from lacking interval properties these scales do not have a true zero, the *sine qua non* of ratio scales. Indeed, the EQ-5D-3L can take negative values (range -0.59 to 1.00). This allows, interestingly, for negative I-QALYs. The same argument applies to your previous report on Emicizumab, although in this case, if I read you correctly, you lump together in the model, utilities from different instruments (they all have ordinal properties). They are not equivalent [4].

Unfortunately, the draft evidence report for hemophilia A, with the model developed by staff in the College of Pharmacy Modelling Group, University of Illinois also believe (or at least have an understanding) that the EQ-5D-3L utility scale has 'ratio' properties [5]. There is no defense of this position or a proof of this belief. Unfortunately, the authors of the two papers used to support the Illinois 'ratio' utilities are also ratio believers. The O'Hara et al paper provides an extended regression modelling exercise (with a serious typo as they copied from a companion paper [6]: the dependent variable defined as 'non-drug related direct costs') to generate EQ-5D-3L index scores by target joint status (means and standard deviations; Table 2) . Unfortunately, as the utility scale created by the EQ-5D-3L is ordinal, where we have no idea of the 'distances' between the scores; we can only rank them. The only measures allowed are medians and modes and the application of non-parametric statistics. The Ballal et al paper provides simulated EQ-5D-3L scores for a typical patient with and without knee surgery [7]. The paper then goes on to present mathematically impossible or I-QALYs arguing for surgery as the preferred strategy. Again, we have authors who believe in the 'ratio' utility scale.

You may recall that in the public comment window for ulcerative colitis, I raised a number of questions designed to establish the basis for your belief in the ratio scale property of the EQ-5D; specifically your ability to provide a proof of this claim. Your response to these questions indicated that you could not provide a proof. Your response reads:

We (and most health economists) ***have the understanding*** *(emphasis added) that the EQ-5D (and other multiattribute instruments) do have ratio properties. The EQ-5D value sets are based on time trade-off assessments (which are interval level) with preference weights assigned to different attributes. We fail to see why this should be considered as an ordinal (ranked) scale. ICER believes that the dead state represents a natural zero point on a scale of health related quality of life. Negative utility values on the EQ-5D scale represent states considered worse than dead.*

I have just published a comment on this rather strange response [8]. It reads:

This is a truly amazing response; and one that is demonstrably false. For ICER everything in constructed simulations is by assumption. ICER and others may assume anything; in this case to assume the TTO tariffs of the EQ-5D algorithms have ratio properties is complete nonsense. Unfortunately, ICER does not provide a proof of this bizarre assertion. Similarly the TTO

technique does not yield interval let alone ratio properties[9] . The TTO tariffs created by the EQ-5D scoring formulas from the econometric modelling have only ordinal properties.

If ICER continues to insist that they can defy the axioms of fundamental measurement they are entitled to do so; hoping presumably that they will be believed. If, as discussed in the text, ICER insists on this ratio property then the EQ-5D-3L with a range from -0.59 to 1.0 must have (somewhere) a true zero. However, ICER, in their reformulation of measurement theory must prove that in the absence of a true zero multiplication (to create QALYs) is possible. Can we see this proof? This proof must support all arithmetic operations (but not be assumption). However, we do have the intriguing but weird possibility of negative QALYs! I suppose there is an upside.

Consider the phrase 'have the understanding'. Can health economists demonstrate that the EQ-5D-3L, even with negative values, has ratio properties which requires a true zero? Can ICER show that time-trade off has unidimensionality and interval properties? The answer is that it does not: to claim that the EQ-5D-3L scale has ratio properties because the TTO has interval properties is just nonsense. ICER might demonstrate how an interval scale can be (and apparently has been) transformed to a ratio scale. We might have the understanding that the moon is made of green cheese; this does mean it has. At least this claim can be empirically assessed unlike ICER claims.

Indeed, ICER admits that there can be states worse than dead (i.e., negative utilities) which means that the scale does not have ratio properties. Perhaps ICER should make its mind up.

As detailed in a number of my publications, the I-QALY is an impossible construct which means, by extension, that your reference case value assessment framework is invalid [10] . It is up to you, but I would think you should advise your audience in ICER subscribers and the various formulary assessment groups, and PBMs of these limitations on your modelled recommendations.

In any event, I would like a response to two questions (let's avoid *have the understanding*). These are:

(i) Do you have a proof that the EQ-5D-3L/5L have ratio measurement properties; and
(ii) Do you have a proof that the TTO has interval measurement properties

Yours sincerely

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SANOFI GENZYME

September 23, 2020

Catherine Koola, MPH
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Dear Ms. Koola,

Sanofi Genzyme would like to acknowledge the scientific work conducted by ICER and welcomes the opportunity to provide feedback on the Draft Evidence Report entitled, "Valoctocogene Roxaparvovec and Emicizumab for Hemophilia A: Effectiveness and Value".[1]

We reviewed the report in detail and have several concerns surrounding the transparency of the methodology, inappropriate assumptions, and generalizability of the conclusions that warrant careful consideration. The most relevant comments are summarized below, separated by the section of the ICER report they address.

Section 4. Comparative Clinical Effectiveness

1) **Network Meta-Analysis (NMA):**

The NMA generalized all FVIII treatments based on a single study (SPINART- NCT00623480) representing a single FVIII product [rFVIII-FS: Kogenate® FS Antihemophilic Factor (Recombinant)].[2] Based on the pharmacokinetic and dosing profile, this agent is categorized as a standard half-life (SHL) FVIII product.[3] More recently available FVIII agents, categorized as extended half-life (EHL) products, contain modifications to their structure that allow for extended duration of action and less frequent dosing, which may affect the patient experience and treatment adherence.[3-6]

Using rFVIII-FS as a proxy for the entire FVIII drug class is a misleading assumption that fails to distinguish significant differences between both the EHL and SHL classes, as well as the individual drugs themselves. Iorio, et al. illustrated these differences when conducting an indirect treatment comparison (ITC) of rFVIII Fc fusion protein (rFVIIIFc) and conventional, or SHL, rFVIII products in hemophilia A patients. They found that prophylaxis with rFVIIIFc may be associated with improved bleeding rates and lower weekly factor consumption than more frequently injected rFVIII products. When comparing to rFVIII products with similar bleeding rates, the authors found that rFVIIIFc may be associated with lower weekly FVIII consumption rates while requiring fewer prescribed injections.[7] Additionally, the presence and method of collecting joint health data further differentiates FVIII agents. For example, Kogenate

assessed joint health using index joint magnetic resonance imaging (MRI) scores of osteochondral damage, while rFVIIIFc collected joint health data for both children and adults in the A-LONG and follow-on ASPIRE studies, leveraging the Hemophilia Joint Health Score (HJHS) for children under 12 years old, and the modified HJHS for use in population aged 12 or older.[8-10]

Therefore, the generalization between EHLs and SHLs, and the exclusion of data that differentiates each product's unique profile, may lead to the inaccurate interpretation of results. Given this significant limitation, ICER should clearly state in its report, that the results of the clinical comparison to emicizumab, and the corresponding evidence rating, are only applicable to rFVIII-FS alone. Additionally, as the results of the NMA are incorporated into the cost-effectiveness model, the output of that analysis should also only be applicable to rFVIII-FS and should be stated as such.

2) Comparative Net Health Benefit

The conclusions in the comparative net health benefit section are misleading and inaccurate, and do not align with the findings of the NMA. The NMA results show that there is **NO** significant difference between emicizumab and rFVIII-FS when evaluating treated bleeds and treated joint bleeds. However, the summary results of the comparative net health benefit section of the Evidence Report do not align with this finding. The authors conclude that there is a difference simply because the bleeding rates were numerically lower for emicizumab. Additionally, as only treated bleeds (including treated joint bleeds) were the only bleeds evaluated, the statement "…appears to have lower bleeding rates (of all types) compared with factor VIII..." is incorrect.

Section 5: Long-Term Cost Effectiveness

1) Limitations of Pettersson Joint Health Score

The utilization of the Pettersson joint health score warrants a disclosure of the limitations of this measure**.** While the first ICER modelling approach accurately captures possible bleeding stages (overall vs target joint / treated vs untreated) and the subsequent consequence of repeated bleeds (arthropathy estimated via Pettersson joint score), the new proposed structure focuses heavily on tunnel stages of arthropathy using the same score.[11] We agree that the use of the Pettersson score in economic models represents the most pragmatic approach to assess joint damage, considering the limitations of existing endpoints/measures. Stages built entirely using this score presume however that a) point categories in the score are related to a specific cost and utility of patients using literature proxies (PS = 0, PS 1-27 or PS = 28), which contrasts with the natural intuition to attribute costs and disutilities to each bleed type as occurring in real clinical setting b) no distinction between joint and non-joint bleeds and c) treated and untreated arthropathy

patients have a similar risk to develop degenerative arthritis, which neglects the clinical benefits of early treatment of chronic hemarthrosis.

2) Lack of Pediatric Data

In the Heterogeneity and Subgroups section of the report, the authors identify that there is insufficient data to conduct a comparison between emicizumab and FVIII therapy in children. However, in the cost-effectiveness model, the age of the cohort begins at one year old. As a large percentage of prophylaxis treatment in Hemophilia A patients starts at a young age, it is understandable that there is a need to evaluate the cost-effectiveness of this population. However, given the limited data comparing FVIII and emicizumab in this population, we do not think that the model should extrapolate the results to include an age group not supported by data. Therefore, we recommend that the model start evaluation at 12 years old.

3) Scenario Threshold Analysis

We have several concerns in terms of the assumptions and inputs that are incorporated into the scenario threshold portion of the modeling scenarios. They are as follows:

a) Use of Rurioctocog alfa (recombinant factor VIII: Advate®) and recombinant factor VIII Fc (rFVIIIFc) (Eloctate®) as "representative" of the standard half-life (SHL) and extended half-life (EHL) classes, respectively.

Given the fact that the comparative effectiveness / NMA components of this evidence report are based on data from one clinical trial and a single SHL FVIII therapy [rFVIII-FS: Kogenate® FS Antihemophilic Factor (Recombinant)], the cost-effectiveness model should only reflect that specific FVIII therapy. To extrapolate clinical findings from one factor therapy to two entire classes of FVIII agents discards the wealth of data that differentiates these products. Furthermore, the inclusion of drug costs and dosing data from two separate agents, not included in the comparative effectiveness assessment, is misleading and erroneous.

b) Inclusion of real-world dosing data into the cost-effectiveness modeling scenarios

While real world evidence (RWE) is an important component of any assessment of drug therapy, the arbitrary inclusion of dosing data on Advate and Eloctate should be removed for several reasons, specifically:

I. As stated above, these agents were not part of the comparative effectiveness analysis

II. There is no mention of planned incorporation of real-world dosing data in the modeling analysis plan (MAP) for this evidence report .[12] The MAP also states that the HAVEN 3 trial will be used as the source for representative treatments, originally listing a breakdown of 87% SHL and 13% EHL. This ratio differs from the 71.18% SHL and 28.82% SHL used in this draft evidence report.

III. Per ICER's own recommendations and publications on inclusion of RWE into coverage decisions, there needs to be a transparent and systematic process for evaluation and utilization of such data.[13-15] There was no such process followed in regard to the inclusion of the unreferenced, American Thrombosis and Hemostasis Network (ATHN) dosing data. A comprehensive literature search would have identified many RWE studies on FVIII therapy demonstrating a range of doses. [10, 16-19] While of good quality, the ATHN data should not be considered as reflecting the typical treatments and dosing patterns for all Hemophilia A patients. The data from ATHN is representative of a hemophilia treatment center (HTC) focused population of patients. Dosing of FVIII therapy can be impacted by many things such as age (child/adult), severity of hemophilia, prophylaxis/on-demand, inhibitor status and other patient related factors.

IV. If RWE is to be incorporated into these analyses, all outcomes should be evaluated for inclusion, not just dosing. For example, real-world data on clinical effectiveness, safety and costs could considered for inclusion. Regardless of the type of data included, an open, systematic and comprehensive review is required.

We appreciate ICER's consideration of our feedback and welcome additional discussions with ICER to address any questions that may arise.

Sincerely,

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September 23, 2020

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RE: Takeda Response to the Draft Evidence Report "Valoctocogene Roxaparvovec and Emicizumab for Hemophilia A: Effectiveness and Value"

Takeda appreciates the opportunity to provide comments during this open period regarding the August 26th draft evidence report to assess the effectiveness and value of gene therapy and emicizumab for hemophilia A.

Takeda Pharmaceutical Company Limited (Takeda) is a global, value-based, R&D-driven biopharmaceutical leader, committed to bringing better health and a brighter future to patients by translating science into highly innovative medicines. Our R&D efforts focus on four therapeutic areas: Oncology, Gastroenterology (GI), Rare Diseases (including bleeding disorders) and Neuroscience. Takeda also makes targeted R&D investments in Plasma-Derived Therapies and Vaccines. Takeda focuses on developing medicines that contribute to making a difference in people's lives by advancing the frontier of new treatment options.

Takeda is a leader in hemophilia with the longest heritage and a market-leading portfolio, backed by established safety and efficacy profiles with decades of real-world experience. We have 70+ years of experience driving innovation for patients and a broad portfolio of 11 products across multiple bleeding disorders. Our experience as leaders in hematology means we are well prepared to meet today's needs as we pursue future developments in the treatment of bleeding disorders. Together with the hematology community, we are committed to raising expectations for the future, including earlier diagnosis, earlier and better protection against bleeds, and more personalized patient care.

And while Takeda is proud of our long history, Takeda is also excited about what lies ahead. Dedicated to purposeful progress, Takeda is on a mission to transform the future treatment of bleeding disorders and other blood disorders. Our vision for a bleed-free world fuels our passion every day to make a difference in the lives of those with bleeding disorders.

In response to the ICER draft evidence report regarding the effectiveness and value of gene therapy and emicizumab, Takeda is highlighting three areas of concern below including recommendations for consideration as ICER updates their evidence report.

Takeda Recommendations for ICER Consideration

1. Reconsider the B+ evidence rating based upon non-significant results of the indirect comparisons and improve the reporting of uncertainties and limitations
2. Replace the term "more representative" to "alternative dosing scenario" when referring to the scenario analysis and further explain variability in weekly FVIII utilization
3. Present the conclusions in a more balanced manner by highlighting both base case and scenario analyses and why a "one-size-fits-all" dosing assumption may not be appropriate

1) Indirect Comparison Evidence Rating of Emicizumab vs Factor VIII (FVIII)

Because of the lack of head-to-head clinical trials between emicizumab and FVIII, generation of comparative efficacy evidence and the resulting assessment of alternative treatments require the use of indirect comparisons. As a result, one must appropriately weigh the strength of that evidence when drawing conclusions based on these comparisons. To that end, Takeda has several comments on the current draft and ask ICER to consider our recommendations.

a. Deviation from a priori decision to use random effects model

Takeda agrees with ICER's a priori decision in the protocol to prefer the random effects network meta-analysis (NMA) due to differences in the study populations. However, results from the fixed effects model were used to estimate uncertainty in the sensitivity analyses and seemingly used to interpret ICER's evidence grade for emicizumab. While the point estimates for the rate ratios for bleeds are equivalent under the fixed and random effects models, the estimated standard errors are lower (and the resulting confidence intervals are narrower) under the fixed effect model. In this particular case, the conclusion regarding statistical significance differs between the models. **Since the random effects NMA was decided as the preferred model a priori**, **Takeda recommends that ICER utilize the credible intervals from the random effects model when conducting the one-way and probabilistic sensitivity analyses and also consider the lack of statistical significance when determining the evidence rating.** Because of the wider intervals with the random effects NMA compared to the fixed effects model, uncertainty in the model-based results should be greater than currently reported.

b. Underreporting of fundamental heterogeneity and lack of consideration of uncertainty in determining strength of comparative evidence

While HAVEN 3[1] and SPINART[2,3] are well-designed studies, they have fundamental differences in design, populations, and outcome definitions. Since SPINART was specifically

investigating secondary and tertiary (late) prophylaxis, it included a patient population that was not on regular prophylaxis therapy for ≥12 months over the previous 5 years.[2,3] This requirement alone creates a population that is likely to be systematically different than a population that does not have that requirement. For example, patients included in SPINART may have poorer control over their bleeds due to foregoing any proactive continuous prophylaxis and/or they may have compromised joint integrity due to the nature of more frequent bleeding observed with episodic therapy which may lead to more recurrent bleeds during the investigation period. These differences introduce the risk of bias and uncertainty, which is not currently discussed in length in the draft report. **Takeda recommends that several aspects of heterogeneity be highlighted in the report and how that impacts the strength of conclusions that may be drawn**.

c. Patient subjectivity involved in outcome reporting, differences in outcome definitions, and impact of differences in follow-up periods

A critically important issue we identified is the use of 'treated bleeds' as the outcome of interest instead of 'all bleeds'. This methodological decision is understandable considering the healthcare sector perspective. However, it limited the number of FVIII pivotal trials that met the inclusion criteria, thereby increasing uncertainty of bleed estimates for FVIII products. Treated bleeds were not reported in SPINART's 1-year follow-up and were only reported in the 3-year follow-up.[2,3] While the population in the two follow-up analyses are the same, their bleed rates differed at the different follow-up times. In the 1-year follow-up analysis of SPINART, the mean **total** number of bleeds (standard deviation [SD]) were 2.0 (4.5) while the mean **treated** bleeds (SD) in the 3-year follow-up were 2.5 (4.7). Rate of total bleeds would be expected to be higher than treated bleeds, considering total bleeds include both treated and untreated bleeds, which was not observed. This may illustrate the progressive nature of severe hemophilia A or loosening of heavily controlled pivotal trial requirements during long-term follow-up. Regardless, it highlights the impact follow-up time may have on bleed outcomes and how it may be inappropriate to assume annualizing bleed rates adequately control for differences in follow-up times between trials (HAVEN 3 [24 weeks] vs SPINART [3 years]), **Therefore, in order to include more evidence from FVIII trials and utilize more comparable follow-up periods, we recommend either the use of all bleeds to conduct indirect treatment comparisons, or more transparent reporting of the limitations and uncertainties inherent when comparing 1) bleed outcomes based on subjective patient decision to treat a bleed and 2) bleed rates over differing follow-up periods.**

d. Selection bias in HAVEN 3 intra-individual comparison confounding its use to support evidence rating[1]

HAVEN 3 intra-individual comparison of patients who previously participated in a non-interventional trial may not be accurate and reliable and is not an appropriate source of evidence to support differences in efficacy between emicizumab and FVIII replacement

therapy. The non-interventional trial design is at very high risk of selection bias as investigators may have selected participants for inclusion who were poorly controlled, experiencing frequent bleeds while on FVIII therapy, and/or who would be thought to benefit from switching to emicizumab compared to the overall population[4]. Kruse-Jarres, et al. raise this important consideration in their discussion[4]. Lack of adherence observed in the non-interventional trial support the presence of selection bias; this population may represent patients who were unsuccessful on FVIII treatment as opposed to the overall population of interest in this review.

e. Final Recommendation

Takeda believes the B+ evidence rating for emicizumab ignores the inherent heterogeneity within the indirect comparison, lack of uniform outcome definition, and lack of statistical significance in the random effects NMA. Based on the ICER Evidence Rating Matrix, a B+ rating assumes the lower end of the confidence interval does not extend into the comparable range. While the "comparable range" was not defined, the confidence intervals for the annualized treated bleed rate ratio and the annualized treated joint bleeds rate ratio for emicizumab vs FVIII prophylaxis both include 1.0 (see Tables 4.4 and 4.5 from the draft evidence report, respectively). Thus, one cannot conclude that the two treatments differ with any degree of certainty. Instead, it seems more reasonable to declare a high certainty of a "comparable" efficacy rating based on the consideration of the cumulative topics in this section. Therefore, **Takeda recommends reconsideration of the B+ rating for a lower rating, as evidence illustrates comparability and lacks strong evidence of any differentiation of efficacy.**

2) Scenario Analysis 'Representative' Label

FVIII utilization for prophylaxis varies greatly based on individual patient characteristics.[5,6,7] Stating that one dose is more 'representative' than another ignores the spectrum of utilization across patients. A recent study investigating real-world FVIII consumption illustrates the large variability in weekly FVIII consumption among patients with severe hemophilia A on prophylaxis.[8] Additionally, evidence demonstrates that adult patients consume less FVIII than pediatric patients.[9] Therefore, weekly FVIII consumption may decrease over time. Takeda understands this is a population level analysis and averages are typically used to help make population level policy recommendations; however, the wide variation of FVIII utilization among patients may make it inappropriate to make 'one-size-fits-all' interpretations. **Takeda recommends relabeling this scenario as an 'alternative-utilization scenario' rather than one that is "more representative" to prevent confusion that a single dosing average represents an entire population.** Payers should make policy decisions regarding the role of FVIII for patients based on individual utilization of FVIII. Stating the cost-effectiveness results based on a FVIII dose of 118.2 and 111.2 IU/kg/week as "more representative" may have significant economic consequences if the scenario analysis is interpreted as 'the truth' and is applied to all patients regardless of their actual FVIII utilization.

Also, it is understood the American Thrombosis & Hemostasis Network was used to determine alternative dosing averages, however, it is largely unclear how the 118.2 IU/kg/week for ADVATE and 111.2 IU/kg/week for ELOCTATE were derived. For example, was FVIII utilization for breakthrough bleed treatment included in the average weekly dosing and what was the mean age? **Takeda recommends improved reporting of scenario analysis dosing elicitation to better understand the methods and to promote replicability.**

3) Contradicting Conclusion Raises Confusion about 'Correct' Interpretation

While the "Summary and Comment" section of the report begins each comparison with the base case result, the emphasis quickly shifts to highlight the results of the scenario analysis which have contradicting results. Interpreting both conclusions independently without explaining the individualized and dynamic dosing of FVIII may lead to confusion and misunderstanding of the results, especially for an audience that may not be technically trained in health economics. Thus, **Takeda recommends that ICER consider presenting the conclusions in a more balanced fashion and further explain the dynamics of variability in dosing and how that may impact conclusions to prevent confusion on which results are 'correct'.**

Takeda appreciates the opportunity to participate in the scientific dialogue while ICER continues to prepare the evidence report for hemophilia A therapies. As a leader in the hemophilia and bleeding disorder field, Takeda believes the above recommendations will lead to a stronger scientific and objective report that will ultimately help inform policy recommendations based on the value of available treatment options for patients living with severe hemophilia A.

Kind Regards,

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