Adult lifetime cost of hemophilia B management in the US: payer and societal perspectives from a decision analytic model

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ABSTRACT
Aims: Hemophilia B (HB) is a rare congenital disorder characterized by bleeding-related complications which are managed by prophylactic or post-bleeding event (“on-demand”) replacement of clotting factor IX (FIX). The standard of care for severe HB is life-long prophylaxis with standard half-life (SHL) or extended half-life (EHL) products given every 2–3 or 7–14 days, respectively. FIX treatment costs in the US have been investigated, but the lifetime costs of HB treatment have not been well characterized, particularly related to the impact of joint health deterioration and associated health resource utilization. We developed a decision-analytic model to explore outcomes, costs and underlying cost drivers associated with FIX treatment options over the lifetime of an adult with severe or moderately severe HB.

Materials and methods: With participation from clinicians, health technology assessment specialists and patient advocates, a Markov model was constructed to estimate bleeding events and costs associated with health states including “bleed into joint”, “bleed not into joint”, “no bleed” and “death”. Sub-models of joint health were based on 0, 1, or ≥2 areas of chronic joint damage. US third-party payer and societal perspectives were considered with a lifetime horizon; sensitivity analyses tested the robustness of primary findings.

Results: Total adult lifetime costs per patient with severe and moderately severe HB were $21,086,607 for SHL FIX prophylaxis, $22,987,483 for EHL FIX prophylaxis, and $20,971,826 for on-demand FIX treatment. For FIX prophylaxis, the cost of FIX treatment accounts for >90% of the total HB treatment costs.

Conclusions: This decision analytic model demonstrated significant economic burden associated with the current HB treatment paradigm.

Introduction
Hemophilia B (HB) is a rare congenital blood disorder characterized by deficiency of clotting factor IX (FIX) with spontaneous bleeding episodes, most notably into joints, and delayed hemostasis in external bleeding events. There are approximately 6,000 people with HB in the US, with an estimated incidence of one per 20,000 live male births. Recurrent bleeding into joints can cause long-term joint deterioration resulting in physical impairment, the need for joint replacements, chronic pain, and reduced quality of life (QoL). The severity of HB is defined by the level of circulating FIX and management is based on FIX replacement therapy administered either prophylactically to prevent bleeding episodes or after a bleeding episode has occurred, known as “on-demand” treatment. The standard of care for patients with severe and moderately severe HB is FIX prophylaxis. FIX supplementation is given intravenously as using standard half-life (SHL) or extended half-life (EHL) treatments, which are given every 2–3 or 7–14 days, respectively. The frequent infusions required by FIX treatment incur a level of treatment burden that can compromise adherence and clinical effectiveness. People with mild or moderate HB who tend to experience relatively infrequent bleeding episodes are often managed with on-demand FIX treatment in order to minimize treatment burden.

FIX prophylaxis is effective in reducing the frequency of bleeding events and improving morbidity and mortality for patients with HB. However, the cost of treatment is substantial. The mean annual cost of FIX prophylaxis for HB in the US has been reported to be $610,966, ranging from $397,491 to $788,861 for people with HB using SHL and EHL.
A hypothetical cohort of male adults (≥18 years old) with severe and moderately severe HB and no history of inhibitors entered the model. Three treatment options were included: SHL FIX prophylaxis, EHL FIX prophylaxis, and on-demand FIX treatment. SHL FIX prophylaxis was based on the use of nonacog alfa; other SHL products have limited real-world usage in the US and were excluded. EHL FIX prophylaxis included albutrepenonacog alfa, efmab, and nonacog beta pegol. On-demand FIX treatment included both SHL and EHL products. For each treatment arm, the number of bleeding episodes and joint bleeds occurring within the lifetime horizon of the model were recorded. Costs and benefits were discounted at an annual rate of 3%, which is standard in US economic models and in line with the Institute for Clinical and Economic Review (ICER) Value Assessment Framework. The model considered both US third-party payer and societal perspectives, where the payer perspective focused on direct medical costs and the societal perspective also included non-medical costs (resources supporting healthcare sector services) and indirect costs (e.g. productivity losses). The decision analytic model was developed in Microsoft Excel (Redmond, WA).

**Model framework**

The Markov cohort model (Figure 1) was constructed with mutually exclusive health states based on naturally occurring events during the lifetime of people with HB. The health states included in the model were: “No bleed”, “Bleed (not joint)”, “Bleed (joint)”, and “Death”. All patients began in the “No Bleed” health state and could transition over time to a “bleed” event or “dead” health state. Depending on the type of bleeding episode, patients transitioned to either “Bleed (joint)” or “Bleed (not joint)” based on the weekly transition probability, derived from the annual bleed rate (ABR) reported in clinical trials for each arm. The probability of death at the given point of time in the model was calculated based on age-specific male general population mortality in the US. A one-week cycle length with half-cycle correction was employed. As advised by the expert panel, a lifetime horizon was applied in the base case analysis. Shorter time horizons were tested in scenario analyses for 3, 5, and 10 years.

In order to quantify the impact of bleeding rate on joint damage over time, three sub-models were defined using the current number of problem joints (PJs) acquired. PJs are a measure of chronic joint damage and defined by symptoms such as limited range of motion, pain, and hemophilic arthritis. According to the expert panel, this definition was deemed a better representation of long-term joint health than the target joint (TJ) definition, which is defined as three bleeding events into a given joint during a 6-month period. It was recognized that the burden associated with repeated bleeding would be captured by the main model structure, as this was based on bleeding events. In each model cycle, to reflect progressing joint deterioration, a proportion of patients irreversibly moved from 0 PJ through 1 PJ to ≥2 PJs sub-models (Figure 1). The distribution of the
cohort across joint damage sub-models at model entry was assumed to be 80% for 0 PJ, 10% for 1 PJ, and 10% for 2+ PJs. The probability of transition between PJ sub-models was based on Fischer et al.\textsuperscript{23}, where 12.6 joint bleeds on average generated an increase in Pettersson score and reflected progression in the deterioration of joint health. Based on this assumption, the weekly probability of transition to the next PJ sub-model was calculated considering annual joint bleed rate (AJBR) of each treatment arm.

**Model inputs**

The base case model inputs and ranges of model inputs used for sensitivity analyses are summarized in Table 1. All costs were translated to 2019 USD($) and adjusted to the length of the weekly treatment cycle as appropriate. Annual bleed rates and AJBRs were based on the pivotal trial results of the FIX products and used to calculate non-joint bleed rates. It was assumed that patients in the 1 PJ and 2+ PJs sub-models could undergo an orthopedic surgery once or twice per lifetime (between the ages of 45 and 89 years), respectively\textsuperscript{16,17}.

Prophylaxis and on-demand dosing information was based on US prescribing information (US PI) for FIX products. The unit price for FIX products was based on the wholesale acquisition cost (WAC), as reported in Redbook. The dose per infusion of FIX therapy was calculated using national average weight in the US, using published weight tables\textsuperscript{28} for the age-matched US male population. Market research data on real-world usage were used to derive the treatment mix of people with HB using alternative EHL products in the EHL prophylaxis arm and of people with HB using SHL and EHL products in the on-demand arm\textsuperscript{19}. Data from five clinical trials\textsuperscript{8,9,24,29,30} across SHL and EHL products were used to calculate an average of 1.2 FIX infusions needed to treat a bleeding event.

Non-drug costs of HB management included hospitalizations due to bleeding, orthopedic surgery, or intracranial hemorrhage, and outpatient visits. The frequency and average length of stay of bleed-related hospitalizations and the frequency of office visits were derived from the CHESS US.
The unit cost for hospitalization and office visits were sourced from literature and the CMS Physician Fee Schedule. Non-medical costs included expenses incurred due to travelling to the HTC and were sourced from the CHESS US study. The components of indirect cost included productivity losses and social benefits. The human capital approach was used to estimate productivity losses. Data sourced from the CHESS US(+) study (a patient-centric follow-up study to CHESS US that gathered data on indirect costs of hemophilia) were used to estimate both productivity losses and social benefits cost.

### Sensitivity analysis

Model inputs were tested in one-way sensitivity analysis (OWSA) primarily based on the 95% confidence interval for each parameter. For variables with no available estimates of

| Parameter | Base case estimate | Range | Notes | Reference |
|-----------|--------------------|-------|-------|-----------|
| Clinical inputs | | | | |
| Annual bleed rate (ABR) | | | | |
| SHL FIX prophylaxis | 4.052 | 3.8–4.3 | Mean ABR weighted by the number of patients in nonacog alfa trials | Kavakli et al., Roth et al., Lambert et al. |
| EHL FIX prophylaxis | 2.27 | 2.12–2.43 | Mean ABR weighted by the number of patients in trials | Albutepepenonacog alfa: Santagostino et al.; eftrenonacog alfa: Powell et al.; nonacog beta pegol: Collins et al. |
| On-demand FIX | 33.87 | 33.64–34.09 | Mean ABR weighted by the number of patients in trials | Kavakli et al., Valentino et al. |
| Annual joint bleed rate (AJBR) | | | | |
| SHL FIX prophylaxis | 2.1 | 0.85–3.35 | – | Albutepepenonacog alfa: Santagostino et al.; eftrenonacog alfa: Powell et al.; nonacog beta pegol: Collins et al. |
| EHL FIX prophylaxis | 0.89 | 0.71–1.06 | Mean AJBR weighted by the number of patients in trials | | |
| On-demand FIX | 26.17 | 25.94–26.39 | Mean AJBR weighted by the number of patients in trials | Kavakli et al., Valentino et al. |
| Orthopedic surgery | | | | |
| 0 problem joints | 0 | – | – | Assumption |
| 1 problem joint | 1/lifetime | 0.65–1.43 | – | Assumption |
| 2+ problem joints | 2/lifetime | 1.29–2.86 | – | Assumption |
| CNS bleed | 0.00183 | 0.00118–0.00261 | – | Witmer et al. |
| Dosing | | | | |
| Prophylaxis dose (IU/kg) | | | | |
| SHL | 51.70 | 33.46–73.85 | – | US PIs for nonacog alfa, albutrepenonacog alfa and nonacog beta pegol |
| EHL | 45 | 29.12–64.28 | – | US PIs for nonacog alfa, albutrepenonacog alfa and GlycoPEGylated FIX |
| Prophylaxis frequency (days) | | | | |
| SHL | 3.5 | 2.27–5 | – | Lambert et al. |
| EHL | 7 | 4.53–10 | – | US PIs for nonacog alfa, albutrepenonacog alfa and GlycoPEGylated FIX |
| On-demand dose (IU per kg) | | | | |
| SHL | 100 | 60–100 | – | US PI for nonacog alfa |
| EHL | 60 IU per kg | 60–100 | – | US PIs for nonacog alfa, albutrepenonacog alfa and nonacog beta pegol |
| Costs (US) | | | | |
| SHL (IU) | 1.37 | 0.89–1.96 | Nonacog alfa | Redbook 2019 |
| EHL (IU) | 4.40 | 2.85–6.28 | Albutepepenonacog alfa | Redbook 2019 |
| EHL (IU) | 3.12 | 2.04–4.46 | Eftrenonacog alfa | Redbook 2019 |
| EHL (IU) | 4.00 | 2.59–5.71 | Nonacog beta pegol | Redbook 2019 |
| Hospitalization due to bleed | 11,376.03 | – | Calculated by multiplying the frequency of hospitalization due to bleed by the length of stay and the cost per bed day | Bed day cost: HCUP; Frequency of hospitalization and length of stay: CHESS US |
| Orthopedic surgery | 140,071 | 90,647–200,078 | – | Machin et al. |
| CNS bleed | 106,083 | 6,865–15,129 | – | Patel et al. |
| Outpatient care | | | | |
| 0 PJ | 526 | – | Calculated by multiplying frequencies of individual outpatient services by their cost | Cost: CMS Physician Fee Schedule Frequencies: CHESS US |
| 1 PJ | 826 | – | – | |
| 2+ PJ | 1,237 | – | – | |

Abbreviations. ABR, Annual bleed rate; AJBR, Annual joint bleed rate; CMS, Centers for Medicare & Medicaid Services; CNS, Central nervous system; EHL, Extended half-life; HCUP, Healthcare Cost and Utilization Project; SHL, Standard half-life; US PI: United States prescribing information.

*aAnnual cost.

*bRange calculated as a 95% confidence interval assuming 20% variation in those parameters.

*cBased on the clinically plausible ranges.
certainty, 20% variation was assumed. Further testing was conducted for selected variables (discounting rates, on-demand FIX doses, duration of GTx treatment effect, GTx discount for partial responders and orthopedic surgery age) using specified ranges representing plausible ranges to inform the sensitivity of the outcomes.

**Results**

**Base case results**

Model results showed substantial cost of severe and moderately severe HB management associated with all three treatment options (Table 2). From the societal perspective, the adult lifetime total cost per patient was $21,086,607 for SHL FIX prophylaxis, $22,987,483 for EHL FIX prophylaxis, and $20,971,826 for on-demand FIX treatment. From the payer perspective, the adult lifetime direct medical cost per patient was $21,032,332 for SHL FIX prophylaxis, $22,933,207 for EHL FIX prophylaxis, and $20,934,426 for on-demand FIX treatment. Most of the direct medical cost for HB management was driven by FIX treatment, estimated at $19,754,862 and $22,202,092 for prophylaxis with SHL and EHL, respectively (both accounted for more than 90% of direct medical costs). On-demand FIX treatment accounted for approximately 60% of direct medical costs, at $12,179,003. Non-medical direct and indirect costs constituted a relatively small proportion of the total cost of HB management (from 0.18% to 0.26% in lifetime horizon). When the model was run with shorter time horizons, the total cost per patient ranged from $2.2 million to $2.4 million over 3 years, $3.6 million to $3.9 million over 5 years, and $6.7 million to $7.3 million over 10 years across all three treatment arms (Figure 2).

Patients receiving EHL FIX prophylaxis had the fewest total bleeding events (132) and joint bleeds (52) over the adult lifetime horizon. Patients receiving SHL FIX prophylaxis had 234 total bleeding events and 121 joint bleeds, and patients receiving on-demand FIX treatment had 1,632 total bleeding events and 1,211 joint bleeds (Table 2). Similar trends were observed for total and joint bleed results within the shorter time horizon scenarios (Figure 3).

**Sensitivity analysis results**

One-way sensitivity analysis results were generally consistent with the base case results. Total adult lifetime cost of HB management was most sensitive to variations in the unit cost of FIX treatment, discount rates, and the number of...

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**Table 2. Base case analysis results in US adults with hemophilia B (lifetime horizon).**

| Cost                        | SHL FIX prophylaxis | EHL FIX prophylaxis | On-demand FIX |
|-----------------------------|---------------------|---------------------|---------------|
| Direct medical cost         | $21,032,332         | $22,933,207         | $20,934,426   |
| FIX treatment               | $19,754,862         | $22,202,092         | $12,179,003   |
| Other medical cost          | $1,277,470          | $731,115            | $8,755,423    |
| Total medical direct and indirect costs | $21,086,607 | $22,987,483 | $20,971,826 |
| Total bleeds                | 234                 | 132                 | 1,632         |
| Joint bleeds                | 121                 | 52                  | 1,211         |

Abbreviations. EHL, Extended half-life; FIX, Factor IX; SHL, Standard half-life.

*Includes hospitalization cost (due to bleeding, orthopedic surgery, intracranial hemorrhage) or outpatient care costs.
injections needed to treat a bleeding event, regardless of the treatment arm (Figure 4 for SHL FIX prophylaxis, Supplemental Figures 1 and 2 for EHL FIX prophylaxis and on-demand FIX treatment).

Discussion

This decision analytic model showed substantial costs of managing severe and moderately severe HB across the adult lifetime in the US, exceeding $20 million in all scenarios. Occurrence of bleeding events including joint bleeds persisted despite FIX prophylaxis, which accounted for >90% of direct costs, but were markedly greater for patients receiving on-demand treatment only (10- to 20-times more bleeding events in some scenarios). As FIX treatment costs accounted for so much of the total costs, the model was most sensitive to the unit costs of FIX treatment, discount rates, and the number of FIX administrations required to treat a bleeding

Figure 3. Total bleeds for different time horizons. Abbreviations. EHL, Extended half-life; OD, On-demand; SHL, Standard half-life.

Figure 4. OWSA results for a total cost of SHL FIX prophylaxis in adult life-time horizon. Abbreviations: ABR, Annual bleed rate; IU, International unit; PJ, Problem joint; SHL, Standard half-life.
event. This model illustrated a tangible unmet need related to bleeding events and the need for lower costs to prevent and treat bleeding events, from both societal and third-party payer perspectives.

Our model findings are consistent with published real-world utilization studies that the cost of FIX prophylaxis accounts for >90% of direct medical costs of HB management^{14,33,34}. Moreover, substantial lifetime cost of disease management can be also seen in other rare diseases such as Gaucher disease ($6 million)\textsuperscript{15} and paroxysmal nocturnal hemoglobinuria ($9 million)\textsuperscript{16}.

Our study offers a lifetime perspective on treatment cost drivers, where FIX prophylaxis constituted approximately 95% of total medical costs, regardless of EHL or SHL products used. On-demand FIX treatment costs accounted for roughly 60% of total HB costs, but resulted in much higher rates of bleeding events and a similar overall lifetime cost ($21 million) as either SHL or EHL prophylaxis ($21 and $23 million, respectively). Across the adult lifetime horizon, SHL and EHL FIX prophylaxis were associated with 85–90% reductions in total bleeds (132–234 vs. 1,632 total bleeds) and 90–95% reduction in joint bleeds (52–121 vs. 1,211 joint bleeds) compared to on-demand FIX treatment. Taken together, the model suggested that an on-demand treatment strategy did not confer any meaningful direct cost savings compared to prophylaxis, with non-drug medical costs increasing over the long term likely attributable to poorer clinical outcomes. These findings were consistent with previous cost-effectiveness models\textsuperscript{37–41} in hemophilia A comparing factor VIII prophylaxis with on-demand treatment. The broader view offered by these results also highlights that the residual burden of bleeding events with FIX prophylaxis is significant (134–234 total bleeds, 52–121 joint bleeds), particularly considering progressive joint damage. The limited motion and joint pain associated with hemophilic arthropathy are known to further worsen patients’ QoL and wellbeing, underscoring the persistent unmet medical need in this population\textsuperscript{42,43}. It is well documented that there is the clinical benefit of prophylaxis in bleed prevention, joint health, and improving QoL\textsuperscript{5–7,44}. Recent cost-effectiveness analyses (CEAs) also showed prophylaxis is cost-effective compared to on-demand treatment\textsuperscript{39,40,45–47}.

Additionally, Supplemental Table 1 provides an overview of identified cost-effectiveness studies reporting costs of lifelong hemophilia A management in the US\textsuperscript{17,41,48–50}. The majority utilized Markov models and more recent studies included health states capturing joint deterioration, similar to the approach used for our study. Discrepancies in lifetime costs reported by these studies can be partially explained by differences in follow-up periods (due to patients’ ages when entering the model) and cost categories included in the analyses. Although the majority of costs were associated with FIX treatment costs, the considerable scope and impact of indirect costs and non-medical costs should not be overlooked when assessing the overall burden of HB on patients, their caregivers and society. Based on results from 112 patients across 10 HTCs, the HUGS V6\textsuperscript{14} study captured the impact of HB on absenteeism, presenteeism, productivity levels and overall employment status, as well as unpaid hemophilia-related caregiver time. The study reported a significant impact of HB on employment status and work productivity in the US, indicating that indirect costs constitute 9% of the total HB costs. In contrast, our model focused primarily on direct costs and only managed to capture some non-medical and indirect costs, which accounted for less than 1% of total cost. This disparity might be partially explained by the different indirect cost components considered by both studies.

Cost-effectiveness analyses based on decision analytic models are commonly used by health policy makers to determine the value of novel treatments. Waters and Karpf\textsuperscript{51} postulated that CEA could be used to inform the need for cost control, provision of efficient and effective care, as well as evaluation of alternative payment models. Increasingly, more payers and manufacturers use value-based pricing approaches to determine prices for pharmaceutical products, which allows them to determine a price that reflects health gains generated by the treatment of interest. Decision analytic models play a central role in estimating these parameters. Most payers during reimbursement decision-making focus on the evaluation of direct costs, but in some regions or countries indirect costs are also considered. As shown by this research, in hemophilia the total cost is primarily driven by direct medical costs, but inclusion of the societal perspective may be of paramount importance to the cost-effectiveness of therapies in other conditions that are also associated with substantial impairment of patients’ productivity.

Modern treatment advances to date have offered meaningful improvements over historical therapeutic options in terms of clinical outcomes, life expectancy, and QoL; however, this model has quantified that severe and moderately severe HB still pose a significant burden to payers and society, driven primarily by the high costs of FIX treatment. It should be noted that several novel treatments are in development for HB, including gene therapy, and may be considered in future iterations of this work. Based on available phase 1/2 clinical trial\textsuperscript{52,53} findings, HB gene therapy may provide >90% reduction in FIX usage together with further reductions in bleed rates compared to FIX prophylaxis among patients with severe and moderately severe HB, presenting an opportunity for substantial cost offsets in HB management.

Interpretation of this decision analytic model should consider certain strengths, limitations, and contextual factors. The model framework and assumptions combined published estimates with robust input from a panel of clinicians, HTA specialists, and patient advocates, and was aligned with the approach of a recent ICER model for the evaluation of emicizumab for patients with hemophilia A and inhibitors\textsuperscript{17}. The panel input ensured that detailed model assumptions allowed for close approximation of a natural disease history including relevant clinical events and associated costs. Representatives from clinical, patient, and health policy stakeholders ensured that the perspective and model parameters accounted for their considerations in HB management.

Similarly, our model and the ICER model both attempted to simulate a natural disease progression, with emphasis on
joints deterioration, and used similar approaches for transition probabilities across sub-models of joint health. We utilized a joint health definition of "problem joints" that considered published health outcomes research on the impact of TJs on patients' lives and QoL, whereas the ICER model used a more clinical definition based on the presence of arthropathy. The ICER model also used a structure for bleed-related health states that differentiated between treated and untreated bleeding events. Published data sources used for our model inputs were consistent with other published economic evaluations in hemophilia. The lack of appropriate information about the number of PJs accrued by people with HB at different ages was a limitation to the model. The solution to this problem was to assume a baseline distribution of patients with 0, 1 and 2+ PJs. This distribution was then modified within the scenario analysis and consistent estimates were still generated, indicating the robustness of the model findings. The model did not capture the impact of HB on caregivers, which would have increased the indirect cost estimates.

Patients included in this model represented those at greatest risk of spontaneous bleeds, a pool of patients also frequently represented in clinical trials of FIX treatment candidates, and the annual bleeding rate estimates were based on those from clinical trials. Considering the differences between trial participants and those encountered in regular clinical practice, rates of treatment adherence may have been overestimated, and overall bleeding events and joint bleeds may have been underestimated compared to "real-world" rates in a more heterogeneous population. The model may have underestimated the magnitude of clinical, humanistic, and economic burden both for patients entering the model and as they progressed over time with current standards of care.

To our knowledge, this is the first economic model to assess lifetime health outcomes and costs for adults with HB over the natural history of disease, with particular focus on the impact of long-term joint deterioration. This model demonstrated the significant economic burden of current treatment options that exceeded $20 million in any clinical and treatment scenario. Total direct costs were overwhelmingly driven by FIX treatment costs, yet bleeding events and long-term consequences of accumulated bleeds persisted, including joint deterioration and associated medical management. Indirect and non-medical costs appeared provincial in the shadow of FIX treatment costs, but should not be underrepresented in the holistic calculus of long-term burden of HB and the potential to offer patients long-term relief from the meaningful negative impact on employment and life. Despite advances in the available therapeutic approaches to prevent and treat breakthrough bleeding, notable unmet needs remain to further improve clinical, humanistic, and economic outcomes for patients with HB and society.

**Transparency**

**Declaration of funding**

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**Declaration of financial/other relationships**

NL and EKS are uniQure Inc. employees and shareholders. HCD Economics Ltd were funded by uniQure Inc. to conduct this research. KM, GG, MTS, TB, AM and JOH are employees of HCD Economics Ltd. MS reports consulting fees from HCD Economics Ltd. MR has received research support for his institutions from Bayer, BioMarin, CSL Behring, Genentech, Grifols, Hema Biologics, LFB, Novo Nordisk, Octapharma, Pfizer, Sanofi, Spark, Takeda, and uniQure; reports consultant fees from Catalyst Biosciences, CSL Behring, Genentech, HEC Economics Ltd., Hema Biologics, Kedron, Novo Nordisk, Pfizer, Sanofi, Takeda, and uniQure; is on the board of directors of the Foundation for Women and Girls with Blood Disorders and Partners in Bleeding Disorders. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. JME peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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