Valoctocogene Roxaparvovec and Emicizumab for Hemophilia A without Inhibitors: Effectiveness and Value

Final Report

Prepared for

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David Rind served as the lead author for the report and wrote the background, other benefits, and contextual considerations sections of the report. Foluso Agboola was responsible for the oversight of the systematic review and authorship of the comparative clinical effectiveness section with the support of Serina Herron-Smith and Eric Borrelli. Rick Chapman was responsible for the oversight of the cost-effectiveness analyses and development of the budget impact model. Catherine Koola authored the section on coverage policies and clinical guidelines. Surrey Walton and Danny Quach developed the cost-effectiveness model and authored the corresponding sections of the report. David Rind, Rick Chapman, and Steven Pearson provided methodologic guidance on the clinical and economic evaluations. We would also like to thank Monica Frederick for her contributions to this report.

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In the development of this report, ICER's researchers consulted with several clinical experts, patients, manufacturers, and other stakeholders. The following experts provided input that helped guide the ICER team as we shaped our scope and report. It is possible that expert reviewers may not have had the opportunity to review all portions of this report. None of these individuals is responsible for the final contents of this report or should be assumed to support any part of this report, which is solely the work of the ICER team and its affiliated researchers.

For a complete list of stakeholders from whom we requested input, please visit: https://icer-review.org/material/hemophilia-a-update-stakeholder-list/

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List of Acronyms and Abbreviations Used in this Report

AAV5	**Adeno-Associated Virus Serotype 5**
ABR	**Annualized Bleeding Rate**
AEs	**Adverse Events**
ALT	**Alanine Aminotransferase**
aPCCs	**Activated Prothrombin Complex Concentrates**
ASP	**Average Sales Prices**
AST	**Aspartate Aminotransferase**
ATHN	**American Thrombosis and Hemostasis Network**
BSH	**British Society for Haematology**
CEPAC	**Comparative Effectiveness Public Advisory Council**
CID	**Clinically Important Difference**
FDA	**Food and Drug Administration**
NMA	**Network Meta-Analysis**
PICOTS	**Population, Intervention, Comparators, Outcomes, Timing, and Settings**
PRISMA	**Preferred Reporting Items for Systematic Reviews and Meta-Analyses**
PS	**Pettersson scores**
QALE	**Quality-adjusted life expectancy**
QALY	**Quality-Adjusted Life Year**
SAEs	**Serious Adverse Events**
SPEC	**Specialty Drug Evidence and Coverage**
US	**United States**
USHTCN	**US Hemophilia Treatment Center Network**
WAC	**Wholesale Acquisition Cost**
WFH	**World Federation of Hemophilia**
WTP	**Willingness to Pay**

Executive Summary

Background

Hemophilia A is a condition of increased tendency to bleed due to an inherited deficiency of factor VIII, which disrupts the clotting cascade. Hemophilia A has X-linked recessive inheritance, and so predominately affects males. It is the most common of the hemophilias with an incidence of one in 5,000 male births.[1]

Patients with hemophilia A, particularly those with severe disease, are at risk for life-threatening bleeding, including intracranial bleeding, but bleeding into a joint (hemarthrosis) or muscle is more common and can lead to substantial disability.[2] Hemarthroses cause ongoing joint inflammation and damage and also increase the likelihood of further bleeding into the same joint.

To reduce the risk of bleeding, patients with severe hemophilia A have typically administered factor VIII concentrate intravenously multiple times per week.[3,4] The use of factor concentrates both as treatment and prophylaxis has dramatically altered the management and clinical course of patients with hemophilia A. However, prophylaxis with factor replacement is burdensome and does not maintain patients at normal levels of factor VIII. A number of factor VIII preparations are available for prophylaxis, some with modifications to extend the half-life of the therapy, some prepared from human plasma, and some prepared using recombinant technology. Patients can develop inhibitors to factor VIII, but such patients are not considered in this report.

Administration of Factor VIII

Factor VIII concentrate is given intravenously, whether administered on-demand or prophylactically. Prophylaxis is administered multiple times per week, which is burdensome.[5]

Intravenous access requires skill, can be difficult to master and painful, and over many years of treatment accessible veins may clot and no longer be useable. If patients develop arthropathy of upper extremity joints from hemarthroses or become infirm as they age, self-administration of factor concentrate may be more difficult or impossible.

Young children may present particular problems for venous access, both because of an inability to cooperate and because of small veins. For this reason, implanted venous access devices are frequently required for young children. These devices, which include a port placed below the skin, can clot, and can become infected, which typically requires hospitalization to receive intravenous antibiotics and/or to replace the device. Even with such devices, it is generally impractical to initiate prophylaxis until late in the first year of life.

Not surprisingly, adherence to an intravenous therapy that must be administered frequently can be difficult for patients who are appropriate candidates for prophylaxis. Only 50%-70% of patients adhere to prophylaxis regimens, particularly once they are old enough to make treatment decisions for themselves.[6,7]

Emicizumab

Emicizumab-kxwh (Hemlibra®, Genentech, referred to as "emicizumab" in this Report) is a monoclonal antibody with dual targets that allow it to bridge activated factor IX and factor X, the role normally played by activated factor VIII in the clotting cascade.[8] Emicizumab was approved by the US Food and Drug Administration (FDA) as a prophylactic treatment for hemophilia A in patients who have inhibitors to factor VIII in 2017 and in those without inhibitors in 2018.[9] Emicizumab is administered subcutaneously and may be dosed weekly, every two weeks, or every four weeks based on provider and patient preference.

Patients without inhibitors who require treatment for bleeding while receiving emicizumab will generally be treated with a factor VIII preparation as on-demand therapy.

Valoctocogene Roxaparvovec

Valoctocogene roxaparvovec (Roctavian; BioMarin) is an adeno-associated virus serotype 5 (AAV5) mediated liver-directed gene therapy for hemophilia A.[10] Although liver production of factor VIII normally occurs in liver sinusoid endothelial cells, the target of valoctocogene roxaparvovec is hepatocytes.[11] Thus gene therapy with valoctocogene roxaparvovec results in factor VIII production in the liver, but not in the cells in the liver that normally produce factor VIII.

BioMarin submitted a biologics license application for valoctocogene roxaparvovec to the FDA in December 2019 and received a Complete Response Letter (CRL) rejecting approval in August 2020.[12] As a result, ICER considers all results in this report related to valoctocogene roxaparvovec, including results on comparative effectiveness and cost effectiveness, to be highly preliminary.

Insights Gained from Discussions with Patients and Patient Groups

We heard from patients and patient groups that hemophilia can restrict:

- Career choices for the patient and caregivers
- Educational choices for the patient
- Decisions about where to live for the patient and caregivers
- Recreational activities
- Family structure (marriage, divorce, etc.) and employment choices because of concerns about the need to maintain insurance

These generally relate to issues of bleeding risk, being near specialized care, having factor replacement therapy quickly accessible, and having flexible time to deal with bleeding events that can affect choices of both patients and caregivers (Table ES1). Over time, joint injury from bleeding can further restrict patient activities due to pain and inflammation, and in some cases, may require joint replacement surgery. These same joint injuries can eventually limit the ability of patients to care for themselves, as arthritis caused by bleeds may prevent patients from self-administering intravenous infusions.

People with hemophilia may be unable to enter their career of choice; professions that involve manual labor (e.g., farming, carpentry, construction) may involve too great a risk of bleeding. Even people who are employed in professions that do not carry large bleeding risks must ensure that their work keeps them in the proximity of a medical center that is able to provide urgent/emergent treatment.

There is a substantial time burden associated with prophylaxis with factor VIII, as patients who require multiple doses per week must find time for infusions; this can be particularly challenging for caregivers of young and school-aged children, as infusion would need to take place before the school day, and the parent/caregiver's work day, begins. Caregivers of patients who receive infusions through a port must also carefully monitor the port for infection, and such devices may also need to be periodically replaced, and, if they become infected, may require hospitalization for antibiotic treatment, adding to financial and time burdens.

Traditional day care centers are unlikely to be adequately equipped to care for a young child with hemophilia, complicating childcare choices for parents and caregivers. Children may also not be able to participate in common social activities, such as birthday parties, for fear of an accident that causes a bleed.

Table ES1. Reasons for Potential Patient and Caregiver Restrictions Related to Hemophilia A

	Bleeding Risk	Near Specialized Care	Accessibility of Factor	Flexible Time
Caregiver Career		×		×
Patient Career	×	×	×	×
Education		×	×	×
Location of Residence		×	×	
Recreation	×	×	×	

On the issue of a potentially curative therapy for hemophilia, we heard from a patient whose hemophilia was cured by liver transplantation. He noted that this transformed his life in a way that he did not feel he could have completely understood prior to the transplantation and that there was a level of value in this transformation not adequately captured by existing outcome sets for patients with hemophilia.

In response to the Draft Evidence Report, we heard concerns from patients and patient groups that they had struggled to get insurance coverage for dosing regimens of factor VIII that maintain trough levels high enough to adequately control risk of bleeding.

Comparative Clinical Effectiveness

To inform our review of the comparative clinical effectiveness of valoctocogene roxaparvovec gene therapy and emicizumab in the treatment of hemophilia A without factor VIII inhibitors, we systematically identified and synthesized the existing evidence from available clinical studies. Our review focused on clinical benefits, as well as potential harms of these agents compared to each other and to factor VIII prophylaxis. Because valoctocogene roxaparvovec was studied only in adults, we limited our review of this intervention to the adult population.

Valoctocogene Roxaparvovec

We identified 2 publications, 2 conference presentations, and 1 press release regarding two non-randomized trials of valoctocogene roxaparvovec gene therapy (one Phase I/II and one Phase III).[10,13-16] The phase I/II open-label trial involving 15 adults with severe hemophilia A without inhibitors was the key trial; very limited data were available from the phase III trial.

Clinical Benefits

Using factor level classifications (which do not perfectly correlate with clinical severity), severe hemophilia is defined by factor VIII levels below 1% of normal.[17] Patients with severe disease who are not receiving prophylactic treatment experience an average of 20 to 30 episodes of spontaneous bleeding or excessive bleeding after minor trauma per year.[1] Patients with moderate disease (factor VIII levels of 1% to 5% of normal) typically have delayed bleeding episodes after minor trauma several times per year, but only occasionally have spontaneous bleeding.[3] Individuals

with mild disease (factor VIII levels between 6% to 40% of normal) typically have bleeding after procedures such as tooth extractions or surgery, or after significant injuries. Most individuals with factor VIII levels above 40-50% of normal do not have clinical hemophilia.

In the phase I/II trial, all seven participants who received a $6x10^{13}$ vg/kg dose and five out of the six participants who received a $4x10^{13}$ vg/kg dose achieved the pre-specified primary endpoint of factor VIII activity levels of 5 IU/dL or more at week 16.[13] Table ES2 shows the results over four years in the patients receiving the higher dose therapy assessed by two different assays measuring factor VIII activity.

Table ES2. Valoctocogene Roxaparvovec: Factor VIII Activity Over 4 Years in Cohort 3 ($6x10^{13}$ vg/kg) of Phase I/II Study

	Mean FVIII as measured by CS assay			Median FVIII as measured by CS assay		
Follow-up year	Mean (IU/dl)	Δ from previous year (IU/dl)	% Δ from previous year	Median (IU/dl)	Δ from previous year (IU/dl)	% Δ from previous year
Year 1	64	--	--	60	--	--
Year 2	36	-28	↓ 44%	26	-34	↓ 57%
Year 3	33	-3	↓ 8%	20	-6	↓ 23%
Year 4†	24	-9	↓ 27%	16	-4	↓ 20%
	Mean FVIII as measured by one-stage assay			Median FVIII as measured by one-stage assay		
Follow-up year	Mean (IU/dl)	Δ from previous year (IU/dl)	% Δ from previous year	Median (IU/dl)	Δ from previous year (IU/dl)	% Δ from previous year
Year 1	104	--	--	89	--	--
Year 2	59	-45	↓ 43%	46	-43	↓ 48%
Year 3	52	-7	↓ 12%	30	-16	↓ 35%
Year 4†	35	-17	↓ 33%	23	-7	↓ 23%

*CS: Chromogenic.

†measurements based on six of the seven participants (evaluable sample for the 7th participant not available

% Δ: percent change

Using categories of hemophilia, six of the seven participants were in the non-hemophilic range at the end of year one and one was in the mild hemophilic range. The year four data as measured by the more conservative chromogenic assay showed one participant in the non-hemophilic range, four participants in the mild hemophilic range, one participant in the moderate hemophilic range, and one participant back in the severe hemophilic range.[18] The one-stage assay placed two participants in the non-hemophilic range and five in the mild hemophilic range at year four.[18]

Although only limited data are available, gene therapy did not appear to be as successful in the phase III trial. Of the 16 patients who had reached 26 weeks at the time of an interim analysis, only seven had achieved the pre-specified factor VIII levels of 40 IU/dl or greater.[14]

In the higher dose cohort, the mean annualized bleeding rate (ABR) for treated bleeds dropped from a baseline of 16.3 events per year to a cumulative mean of 0.8 per year after four years of follow up, representing a 95% reduction.[10,13,18,19] At baseline, only one participant who had been on

factor VIII prophylaxis had zero bleeding events. Following the administration of valoctocogene roxaparvovec, five out of the seven participants had zero bleeding events in year one of the study; and six out of seven participants had zero bleeding events in years two to four of the study. All participants had full resolution of bleeding in target joints by year two, with continued absence of target joint bleeds in all participants in year 3 (year 4 data not available). In the year before the study, the mean annualized number of factor VIII infusions per year was 136.7; at four years post-administration of valoctocogene roxaparvovec, there was a 96% overall reduction in annualized factor VIII use to a cumulative mean of 5.3 infusions per year.[10,13,18,19]

Haemo-QoL-A evaluates 6 health-related quality of life domains: physical functioning, role functioning, worry, bleeding consequences, emotional impact, and treatment concerns. In the higher dose cohort, a steady improvement was seen in the Haemo-QoL-A total score of participants over four years of follow-up.[19] The mean change from baseline observed over the four years of follow-up matched or exceeded the minimum clinically important difference (CID) of 5.5 points. [19] Data from the Patient-Reported Outcomes, Burdens, and Experiences (PROBE) project designed to evaluate the health status and the health-related quality of life of hemophilia patients shows that patients with milder phenotypes have better general health status and better health-related quality of life.[20] This provides additional indirect evidence for quality of life improvements with gene therapy that places patients into milder phenotypes for a period of time.

Harms

All participants in the Phase I/II trial of valoctocogene roxaparvovec experienced one or more adverse events.[10,13] The most common treatment-related AE was elevation of the alanine aminotransferase level, a marker of liver inflammation, occurring in 86% of patients in the higher dose cohort. All participants developed anti-AAV5 antibodies in the phase I/II study.

Emicizumab

We identified 3 publications and 3 conference abstracts[21-26] regarding three unique Phase III trials (1 randomized and 2 non-randomized) of emicizumab. The key trial was the randomized trial HAVEN 3, which had a primary outcome of ABR for treated bleeds.[21] HAVEN 3 enrolled patients ages 12 and older with severe hemophilia without factor VIII inhibitors; 89 who had not been on prophylaxis were randomized to receive open-label emicizumab or no prophylaxis, and 63 who had been on prophylaxis were treated with emicizumab and compared in a before/after methodology. We identified one randomized trial of factor VIII (SPINART) that was sufficiently similar to HAVEN 3 to permit network meta-analysis (NMA).[27,28]

Clinical Benefits

Table ES3 shows the results from HAVEN 3 and SPINART, Table ES4 shows an NMA comparing the interventions for treated bleeds, and Table ES5 shows an NMA comparing the interventions for treated joint bleeds.

Table ES3. Bleeding Outcomes Reported in HAVEN 3 and SPINART

Bleeding Outcomes	HAVEN 3			SPINART	
	Emicizumab QW	Emicizumab Q2W	No prophylaxis	Factor VIII Prophylaxis	No prophylaxis
Treated Bleeds					
Mean ABR	1.5 (0.9–2.5)	1.3 (0.8–2.3)	38.2 (22.9–63.8)	2.5 (4.7)	37.2 (19.9)
Rate Ratio	0.04 (0.02–0.08)	0.03 (0.02–0.07)	control	0.06 (0.04 – 0.1)	control
All Bleeds (treated + untreated)					
Mean ABR	2.5 (1.6–3.9)	2.6 (1.6–4.3)	47.6 (28.5–79.6)	NR	NR
Rate Ratio	0.05 (0.03–0.10)	0.06 (0.03–0.10)	Control	--	--
Treated Spontaneous Bleeds					
Mean ABR	1.0 (0.5–1.9)	0.3 (0.1–0.8)	15.6 (7.6–31.9)	NR	NR
Rate Ratio	0.06 (0.03–0.15)	0.02 (0.01–0.06)	Control	--	--
Treated Joint Bleeds					
Mean ABR	1.1 (0.6–1.9)	0.9 (0.4–1.7)	26.5 (14.7–47.8)	1.9 (4.1)	28.7 (18.8)
Rate Ratio	0.04 (0.02–0.09)	0.03 (0.02–0.07)	Control	0.06 (0.04-0.12)	control
Treated Target Joint Bleeds					
Mean ABR	0.6 (0.3–1.4)	0.7 (0.3–1.6)	13.0 (5.2–32.3)	NR	NR
Rate Ratio	0.04 (0.02–0.09)	0.03 (0.02–0.07)	Control	--	--

ABR: annualized bleeding rate, FVIII: factor VIII, QW: Once weekly dosing, Q2W: Every 2 weeks

Table ES4. NMA Results of Annualized Treated Bleeds: Rate Ratio (95% Credible Interval)

Emicizumab		
0.57 (0.22, 1.47)	FVIII prophylaxis	
0.03 (0.02, 0.07)	0.06 (0.03, 0.11)	On-demand FVIII

Table ES5. NMA Results of Annualized Treated Joint Bleeds: Rate Ratio (95% Credible Interval)

Emicizumab		
0.53 (0.2, 1.39)	FVIII prophylaxis	
0.03 (0.02, 0.07)	0.07 (0.03, 0.12)	On-demand FVIII

We also identified one observational study conducted in patients with a median age of 8.6 years.[29] Among 39 children without inhibitors in the study, all of whom had been receiving factor VIII prophylaxis, fewer treated bleeds were observed in the six months after initiating emicizumab (ABR: 0.2, 95% CI: 0.0, 0.5) compared to the pre-emicizumab period (ABR: 1.1, 95% CI: 0.5, 2.2)

Similarly, there was a significant increase in the percentage of patients with zero bleeding events in the six months after initiating emicizumab compared to the pre-emicizumab period (94% vs. 73%).

Patients receiving emicizumab in HAVEN 3 had statistically non-significant improvements in quality of life measured with Haem-A-QoL compared with no prophylaxis and had a decrease in days missed from work compared with the 28 days before study entry.[21,26] However, we found no high-quality data allowing us to compare these outcomes between people receiving prophylaxis with emicizumab or factor VIII.

In the before and after comparison done in HAVEN 3, 98% of patients preferred emicizumab over factor VIII prophylaxis.[21] In HAVEN 4, a phase III observational study, all participants who were previously on factor VIII prophylaxis preferred emicizumab over their previous prophylaxis regimen.[23]

Harms

The most common treatment-related AE in HAVEN 3 was injection site reaction, occurring in 25% of patients on emicizumab prophylaxis.[21] Most of the AEs were reported to be mild. Similar patterns of AEs were observed in two other emicizumab trials, with very few serious AEs and those that occurred deemed not to be related to emicizumab.

Uncertainties and Controversies

The evidence on valoctocogene roxaparvovec has multiple limitations creating uncertainties:

- Very few patients have been studied, particularly at the likely dose of $6x10^{13}$ vg/kg
- Duration of follow-up is currently limited and factor VIII levels are declining over time leading to uncertainties in the duration of benefit
- Interim data from the phase III trial suggest lower rates of success in achieving factor VIII levels ≥ 40 IU/dL than in the phase I/II trial, however complete interim data have not been released
- The studies have been single arm with no control group

Valoctocogene roxaparvovec targets hepatocytes rather than endothelial cells, the liver cells that normally produce factor VIII. It is uncertain whether over the long term this could result in chronic liver inflammation or other liver disorders, or if expression could wane in patients with chronic HCV infection whose fibrosis progresses.[30] Concerns have also been expressed in the hemophilia community that low level inflammation related to transfection with AAV5 could lead to long-term liver damage as has been seen with chronic hepatitis C infection and that these harms might take many years to become apparent.

Use of emicizumab in very young children likely affects the rate of development of inhibitors to factor VIII since it precludes the need for prophylaxis with factor VIII, thus reducing exposure, but may increase the likelihood that initial or early exposure to factor VIII will involve higher quantities since those exposures will occur when administration is required to treat bleeding. As discussed in ICER's prior report, the development of inhibitors has very important implications for management, costs, and quality of life. There is no high-quality evidence assessing how emicizumab used in this way affects the rate of inhibitor development. We heard expert opinion that it could increase or decrease the risk of developing factor inhibitors. A randomized clinical trial is comparing emicizumab to factor VIII (Eloctate) in the prevention of inhibitors (see Appendix C).[31]

The RCT evidence on factor VIII that was most comparable to HAVEN 3 comes from a trial that used substantially lower doses of factor VIII than are typically used in the US today. We do not have a randomized trial using these higher doses of factor VIII prophylaxis. As such, the best RCT evidence comparing emicizumab with factor VIII prophylaxis is indirect both because the therapies were studied in different trials and because the dose of factor VIII studied was lower than the appropriate comparator dose. Additionally, within an NMA comparing these therapies, there are wide confidence intervals around the point estimates of effect.

We chose to compare emicizumab with factor VIII prophylaxis using results of each from randomized trials. If reductions in adherence outside of trials are not similar for the two therapies this 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.

Summary and Comment

Valoctocogene Roxaparvovec Compared with Factor VIII Prophylaxis

Current evidence for valoctocogene roxaparvovec has important limitations. We are uncertain about the initial success rate, the initial levels of factor VIII achieved, and the duration of benefit. That said, it is clear that many patients who are successfully treated have their hemophilia signs and symptoms eliminated or reduced to a mild state, at least for a period of years.

Successfully treated patients require no frequent therapies, and so it is far less burdensome than factor VIII prophylaxis. Additionally, adherence to an ongoing therapy is no longer required, although monitoring of factor levels over time remains important.

Liver inflammation can occur acutely with valoctocogene roxaparvovec, but this has typically not been a severe problem. More concerning is the possibility that antibodies to AAV5 could interfere with other treatments including other, perhaps more durable, gene therapies for hemophilia A and treatments or vaccines for conditions such as cancer or infectious diseases.[32,33] An additional

concern is whether therapy with valoctocogene roxaparvovec could lead to chronic liver inflammation, perhaps because the transfected cells are not the cells that normally produce factor VIII.

Overall, there are clear clinical benefits for many patients treated with valoctocogene roxaparvovec, but the durability of these benefits, the implications for disqualification from treatment with other AAV5 therapies, and potential long-term harms such as liver disease are all uncertain. We have moderate certainty of a small or substantial benefit of valoctocogene roxaparvovec compared with factor VIII prophylaxis, but a nonzero likelihood of net harm. As such, in adults with severe hemophilia A without inhibitors, we rate valoctocogene roxaparvovec compared with factor VIII prophylaxis as "promising but inconclusive" *(P/I)*.

Emicizumab Compared with Factor VIII Prophylaxis

Prophylaxis with either emicizumab or factor VIII is far superior to no prophylaxis in patients with severe hemophilia A. Emicizumab appears to have lower bleeding rates (of all types) compared with the doses of factor VIII used in the SPINART randomized trial, perhaps because it avoids the peak and trough levels that occur with factor VIII prophylaxis. We have less certainty in how the efficacy of emicizumab compares with the doses of factor VIII now typically used for prophylaxis in the US. These higher doses have additional efficacy, but the magnitude of that additional efficacy is uncertain.

The long-term comparative effects of emicizumab on joint disease are unknown, both in patients who initiate emicizumab as young children and in adults who initiate it and already have established joint disease.

Emicizumab is substantially less burdensome than factor VIII. Additionally, this may lead to improved adherence and to more patients choosing prophylaxis rather than on-demand therapy.

Although thrombotic events were an issue with emicizumab when patients with inhibitors received large amounts of a bypassing agent for acute bleeding, this has not been noted in patients without inhibitors who are treated with factor VIII for acute bleeding.

We have high certainty that there is at least a comparable net health benefit of emicizumab compared with factor VIII prophylaxis at the doses now typically used in the US, and moderate certainty of a small or substantial net health benefit. As such, in patients with severe hemophilia A without inhibitors, we rate emicizumab compared with factor VIII prophylaxis as "comparable or better" *(C++).*

Valoctocogene Roxaparvovec Compared with Emicizumab

Given the lack of head-to-head evidence comparing valoctocogene roxaparvovec with emicizumab and the uncertainties about valoctocogene roxaparvovec described above, in adults with hemophilia A without inhibitors, we rate the evidence comparing valoctocogene roxaparvovec with emicizumab as "insufficient" *("I")*.

Long-Term Cost Effectiveness

Overview

The primary aim of the economic analysis was to compare valoctocogene roxaparvovec and emicizumab to prophylaxis with factor VIII in patients with hemophilia A without inhibitors to factor VIII who are eligible for prophylactic therapy. We had initially hoped to also compare valoctocogene roxaparvovec and emicizumab to each other, however, as noted in the clinical effectiveness section above, we considered the information insufficient for such a comparison and so evaluated these therapies in separate models.

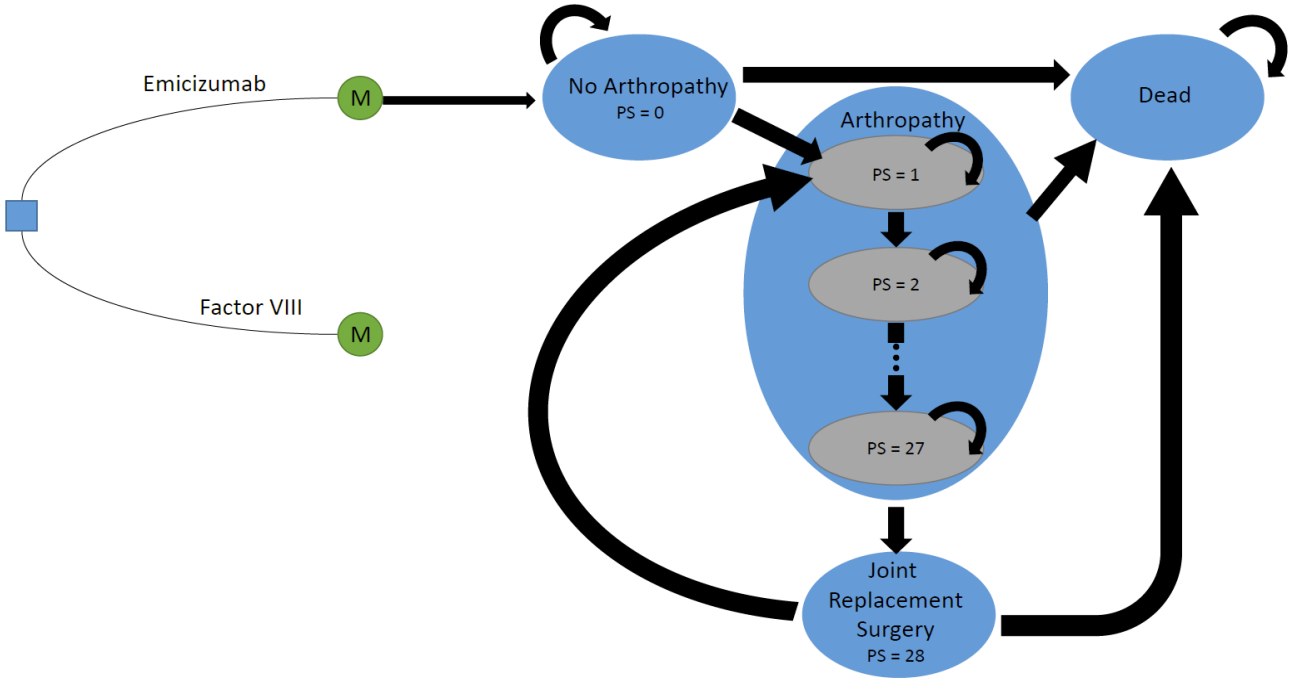
We developed two *de novo* decision analytic models for patients with hemophilia A without inhibitors to factor VIII informed by key clinical trials, prior relevant economic models, and other published studies regarding hemophilia A. The models used a lifetime time horizon and costs, and outcomes were discounted at 3% per year.

The model evaluating the cost effectiveness of valoctocogene roxaparvovec looked only at adult patients and was conducted under the ICER ultra-rare disease framework from a health care sector perspective (i.e., focus on direct medical care costs only); a societal perspective appears as a scenario analysis as the impact of treatment on productivity and other societal costs was not substantial and was not large in relation to health care costs. As valoctocogene roxaparvovec is a one-time gene therapy for hemophilia A, this analysis was also conducted using ICER's High-Impact Single and Short-Term Therapies (SST) framework with additional scenario analyses including optimistic and conservative long-term assumptions and two scenario analyses that shared the estimated net cost savings of a new treatment between the manufacturer and the health care system. In one of these shared savings scenarios, 50% of the modeled cost savings from treatment are "retained" by the health care system instead of being ascribed to the therapy. In the other, cost savings from treatment beyond $150,000 per year are retained by the health care system.

The model evaluating the cost effectiveness of emicizumab looked at patients of all ages with hemophilia A and was conducted under ICER's standard framework, with a health care sector perspective, with productivity and other indirect costs considered in a scenario analysis.

The models focused on acute bleeds and related these to long-term joint damage caused by joint bleeds and the potential need for joint replacement surgery through the use of Pettersson scores (PS) that ranged from 0 to 28 and increased with joint bleeds. Upon reaching a PS of 28, the base case model assumed patients have joint replacement surgery and return to a PS of 1. Transitions through the PS states in the models were based on the expected frequency of joint bleeds associated with the treatments and subsequent expected increases in the PS.[34] In the valoctocogene roxaparvovec model (model 1), patients enter as adults and are modeled as starting with the average PS score seen in patients 18 years of age and consequently none of those patients are ever in the "no joints with arthropathy" health state. In the emicizumab model (model 2), patients begin with a PS score of 0 consistent with being 1 year of age. Figure ES1 below illustrates the structure of model 2; note that model 1 has a very similar structure but patients start with a PS score of 14. In each cycle, the expected number of bleeds across treatments were modeled along with related costs and impacts on patient utilities. Patients remained in each model until death. All patients in both models could transition to death from any of the alive health states.

Figure ES1. Markov Model Schematic for Model 2



M: Markov node, PS: Pettersson score

Costs and utilities were assigned in each cycle based on numbers of different types of bleeds as well as on patient ages and level of arthropathy in the particular health states.

Key Model Characteristics and Assumptions

Below is a list of key model choices:

- Bleed rates determine transition rates across PS, costs, and utilities in the model.
- Bleed rates for valoctocogene roxaparvovec in the first model were derived from available data on factor levels seen in patients on that treatment and literature-based estimates of bleed rates across factor levels.[35] At projected factor levels below 5%, 5% of patients are assumed to switch to emicizumab prophylaxis. At projected factor levels below 1%, all patients were assumed to switch to emicizumab.
- Bleed rates are taken from the HAVEN 3 trial for emicizumab.
- Bleed rates from a recent published study by Malec et al. examining bleed rates in US hemophilia treatment centers affiliated with the American Thrombosis & Hemostasis Network (ATHN) for patients taking factor VIII prophylaxis were used for the factor VIII arms in each model. Given the way bleeds were captured, we view those rates as an evidence-based lower bound for bleeds associated with current dosing.
- Proportions of all bleeds relative to treated bleeds in the HAVEN 3 trial along with proportions of all bleeds that are joint bleeds in the HAVEN 3 and POTTER trials were used to estimate different types of bleeds relative to treated bleeds for factor VIII and valoctocogene roxaparvovec.

Our model also included several key assumptions, stated in Table ES6 below.

Table ES6. Key Model Assumptions

Assumption	Rationale
Total bleeds relative to treated bleeds are modeled based on the emicizumab arm of the HAVEN 3 trial.[21] Joint bleeds were assumed to be the same percentage of all bleeds for each comparator in base case analyses using a simple average of rates of total joint bleeds to all bleeds seen in the various arms of the HAVEN 3 trial (provided by Genentech) and the proportion seen in the POTTER trial (resulting in 0.66 as the proportion used).[36 21]	Treated bleeds are most commonly measured, but total joint bleeds have been shown to impact the PS.[36,37] The POTTER trial offered the only published account of all bleeds and all joint bleeds associated with hemophilia A but previously unpublished data were made available from HAVEN 3 as well. There is no clinical reason to believe that the proportion of bleeds that are joint bleeds, or what proportion of all bleeds would be treated, would vary by treatment, and provided data do not suggest any such difference.
Annual bleed rates are equivalent regardless of the degree of arthropathy.	Data on the relative occurrence of bleed events pre- and post-arthropathy are limited. Increasing bleed rates due to arthropathy are explored in a scenario analysis.
Pettersson scores (representing joint arthropathy development) increase as a function of joint bleeds (treated and/or untreated) over time at different rates for patients over and under the age of 25.	Pettersson scores have most recently been reported to increase by one point for every 36.52 joint bleeds (treated and/or untreated) in patients under 25 and by one for every 6.52 joint bleeds for patients over 25.[37]
The utilities associated with a bleed are applied for two days. After two days we assume the bleed state utility is an average of the no bleed and bleed values for the remainder of a week to reflect that the impact of the bleed on utility lingers after the bleeding stops.	The duration of a bleed is estimated to be two days. However, the impact of a bleed likely lingers beyond bleed duration and treatment time. The number of days per week for bleed utilities is varied in a scenario analysis.

Model Inputs

The rates of bleeds seen in Group B of the HAVEN 3 trial were used for emicizumab. For factor VIII in the base case model, we used doses consistent with current clinical practice, specifically those from the provided ATHN data. We also opted to use bleed rates for factor VIII from a recently published study that included self-reported bleed rates from patients with severe hemophilia A or B being treated in US Hemophilia Treatment Centers affiliated with ATHN.[38] We view this rate to be an evidence-based lower bound of bleed rates associated with factor VIII at currently representative doses.

Treated bleed rates for valoctocogene roxaparvovec were modeled based on available evidence of treated joint bleed rates across factor levels seen in moderate and mild hemophilia patients by den Uijl et al.[35] As shown in Table ES7, bleed rates increase over time with valoctocogene roxaparvovec as factor levels decline until patients are eventually transitioned back to prophylaxis (with emicizumab).

Table ES7. Annual Bleed Rates

Drug	All Bleeds	All Joint Bleeds	Treated Non-Target Joint Bleeds	Treated Target Joint Bleeds
Factor VIII	2.60	1.72	0.60	0.70
Emicizumab	2.60	1.72	0.60	0.70
Valoctocogene Roxaparvovec Year 2	0.45	0.30	0.10	0.12
Valoctocogene Roxaparvovec Year 10	7.05	4.65	1.63	1.90
Valoctocogene Roxaparvovec Year 13	2.60	1.72	0.60	0.70

Baseline utility was taken from results of EQ-5D utilities based on responses from hemophilia patients broken out by age and degree of arthropathy, found in Ohara et al. (Table ES8)[39] All disutilities associated with bleeds and with surgery used in the model were measured in patients with hemophilia A using the EQ-5D.[39-43]

Table ES8. Health State Utilities

Age	Pettersson 0	Pettersson 1-27	Surgery	Source
0-30	0.94	0.82	0.72	O'Hara 2018; Ballal 2011
31-40	0.84	0.74	0.65	O'Hara 2018; Ballal 2011
41-50	0.86	0.69	0.61	O'Hara 2018; Ballal 2011
51-60	0.83	0.63	0.56	O'Hara 2018; Ballal 2011
61-100	0.73	0.54	0.48	O'Hara 2018; Ballal 2011

The utility of surgery is based on one month at a utility of 0.32, and 5 months at a utility corresponding to a Pettersson score of 1-27.

Disutilities by bleed type were estimated based on differences in utilities reported during bleeds versus when having no bleeds, measured in patients with hemophilia A with inhibitors.[40,43] Table ES9 shows the treatment-related cost inputs. For factor VIII, Advate® was selected to represent standard half-life treatment, used by 71.18 % of the patients, and Eloctate® was selected to represent extended half-life treatment, used by 28.82% of patients based on data from ATHN.

Table ES9. Drug Cost Inputs

Drug	WAC per Dose	Discount from WAC*	Add-On Discount	Net Price per Dose†	Net Price per Year‡
Valoctocogene roxaparvovec (Roctavian™)	$2,500,000#	--	0%	$2,500,000#	Not applicable
Emicizumab§ (Hemlibra®)	$100.19/mg	4.7%	6%	$89.33/mg	$569,105
Antihemophilic Factor (Recombinant) (Advate®)	$1.69/IU	18.6%	6%	$1.08/IU	$542,539
Antihemophilic Factor (Recombinant), Fc Fusion Protein (Eloctate®)	$2.23/IU	3.2%	6%	$1.82/IU	$858,026

*Calculated from WAC and ASP

†Net price from July 2020 ASP Pricing File, available at: https://www.cms.gov/medicare/medicare-part-b-drug-average-sales-price/2020-asp-drug-pricing-files, accessed June 30, 2020. From those numbers, $0.23/IU for each factor VIII drug and $0.45 per mg for emicizumab was subtracted along with 6% of the remaining costs to adjust for the portion of costs made up by furnishing fees that would not generally apply.

‡Assumes a weight of 81.4 kg which is the average for an 18-year-old male in the US.

§Maintenance dose

#Placeholder price for valoctocogene roxaparvovec

Non-pharmacological costs from Shrestha et al. were used to inform the direct non-pharmacy related medical costs associated with treated bleeds and treated joint bleeds (Table ES10). The model purposely uses per-bleed costs here to focus on cost reductions associated with reductions in bleeds. Some fixed costs, for example those associated with diagnosis of hemophilia A, are ignored in the model knowing that they would likely be the same across treatments and would not affect incremental cost ratios.

Table ES10. Non-Drug Costs per Bleed by Age

Age (years)	Cost	Source
< 18	$765.48	Shrestha 2017
18-45	$4,604.32	Shrestha 2017
> 45	$6,858.24	Shrestha 2017

In addition to the per-bleed costs, published findings of increased utilization associated with arthropathy were incorporated into the model (Table ES11).

Table ES11. Utilization Related Cost Differences of Arthropathy versus No Arthropathy

	Annual Cost	Source
No Arthropathy	$354.20 per cycle based on office visits and joint related tests	O'Hara 2018 and CMS Fees
Arthropathy	$618.28 per cycle based on office visits and joint related tests	O'Hara 2018 and CMS Fees
Surgery	Arthropathy cost plus $44,717.17*	Earnshaw 2015

*The cost of surgery was derived from Earnshaw et al., which reported a surgery cost of $44,717.17 when inflated to 2019 dollars.[44]

Costs associated with lost time from work for patients and caregivers were estimated based on a burden of illness analysis by Zhou et al.[45] The costs were inflated from 2011 to 2019 by using the total compensation per hour for civilian workers from the Bureau of Labor Statistics. The calculated cost per treated bleed was $1,162.28.

Base-Case Results

Table ES12 describes the discounted lifetime total costs and outcomes from Model 1. In the base-case analysis, valoctocogene roxaparvovec, at its placeholder price, is projected to have lower total costs, lower bleeds, and slightly more QALYs associated with it and thus is a dominant strategy (see Table ES13).

Table ES12. Results for the Base-Case Model Comparing Valoctocogene Roxaparvovec to Factor VIII in Adults*

Treatment	Drug Cost	Total Cost	Joint Bleeds	Treated Non-Target Joint Bleeds	Treated Target Joint Bleeds	Infusions	Life Years	QALYs
Factor VIII (Model version 1 – Health Sector Perspective)	$18,269,000	$18,722,000	68.97	15.92	18.57	3705.17	26.53	19.087
Valoctocogene Roxaparvovec (Model version 1 – Health Sector Perspective)	$13,293,000	$13,693,000	43.70	15.28	17.83	31.06	26.53	19.091

*Results use a placeholder price of $2,500,000 for valoctocogene roxaparvovec

Table ES13. Incremental Cost-Effectiveness Ratios for the Base Case of Model 1*

Treatment	Incremental Cost	Incremental QALYs	Incremental Cost-Effectiveness Ratio
Factor VIII (Model version 1 – Health Sector Perspective)	Reference	Reference	Reference
Valoctocogene Roxaparvovec (Model version 1 – Health Sector Perspective)	-$4,988,000	0.004	Dominant

*Results use a placeholder price of $2,500,000 for valoctocogene roxaparvovec

Table ES14 describes the discounted lifetime total costs and outcomes from Model 2. Emicizumab is projected to have lower costs with the same projected number of bleeds and quality adjusted life years and thus is a cost-saving strategy (Table ES15).

Table ES14. Results for the Base-Case Model Comparing Emicizumab to Factor VIII for All Patients

Treatment	Drug Cost	Total Cost	Joint Bleeds	Treated Non-Target Joint Bleeds	Treated Target Joint Bleeds	Infusions	Life Years	QALYs
Factor VIII (Model version 2 – Health Sector Perspective)	$14,821,000	$15,104,000	38.60	12.64	13.76	4058.67	29.14	24.141
Emicizumab (Model version 2 – Health Sector Perspective)	$13,316,000	$13,598,000	38.60	12.64	13.76	26.41	29.14	24.141

Table ES15 below shows the incremental base case results for Model 2. Emicizumab was found to be highly cost saving with equal projected QALYs.

Table ES15. Incremental Cost-Effectiveness Ratios for the Base Case of Model 2

Treatment	Incremental Cost	Incremental QALYs	Incremental Cost-Effectiveness Ratio
Factor VIII (Model version 2 – Health Sector Perspective)	Reference	Reference	Reference
Emicizumab (Model version 2 – Health Sector Perspective)	-$1,505,000	0.000	Cost Saving

Sensitivity Analyses

In one-way sensitivity analyses, the drug costs and prophylactic drug dosing for the factor VIII products had a substantial influence on the projected incremental costs of valoctocogene roxaparvovec. In probabilistic sensitivity analyses, across thresholds from $50,000 per QALY to $250,000 per QALY, valoctocogene roxaparvovec was a dominant strategy in about 94% of simulations.

In one-way sensitivity analyses, the cost and dose of emicizumab had substantial influence on costs. In addition, the drug costs and prophylactic drug dosing of factor VIII had a substantial influence on the projected incremental costs. In probabilistic sensitivity analyses, in over 30% of the simulations at each of the selected threshold levels emicizumab was found to not be cost effective. These results show that several of the inputs have both sufficient potential variance and influence on the model that there are potential sets of inputs that would give a different conclusion than that seen in the base case.

Scenario Analyses

Scenario analyses that tested a number of different assumptions around bleed duration, bleed rates, joint health after joint surgery, initial age of receiving valoctocogene roxaparvovec, or a modified societal perspective did not alter the conclusions of the base case analysis.

In a set of scenario analyses that used factor VIII doses and efficacy consistent with the NMA conducted in the clinical section, valoctocogene roxaparvovec in model 1 and emicizumab in model 2 were both associated with slightly more QALYs but with very high incremental cost effectiveness ratios.

Under the goals of the ICER SST framework, we performed additional analyses. Under conservative and optimistic scenarios, valoctocogene roxaparvovec, at its placeholder price, remained dominant

over factor VIII. However, in the base case factor VIII levels were projected to remain ≥1% for 12 years, while in the conservative and optimistic scenarios these durations were seven years and 15 years, respectively.

Valoctocogene roxaparvovec, at its placeholder price, also remained dominant over factor VIII when half the net savings were assigned to the health care system, but not when savings were capped at $150,000 per year. These shared savings results are shown in the threshold analyses section below.

Threshold Analyses

Table ES16 shows threshold prices for valoctocogene roxaparvovec that would result in cost-effectiveness ratios of $50,000, $100,000, $150,000, and $200,000 per QALY in the base-case. (Threshold prices do not appear to vary due to rounding.)

Table ES16. Threshold Analysis Results for the Base Case for Valoctocogene Roxaparvovec*

Perspective	WAC per Unit	Net Price per Unit	Unit Price to Achieve $50,000 per QALY	Unit Price to Achieve $100,000 per QALY	Unit Price to Achieve $150,000 per QALY	Unit Price to Achieve $200,000 per QALY
Health Sector	$2,500,000	$2,500,000	$7,490,000	$7,490,000	$7,490,000	$7,490,000

*WAC and net prices for valoctocogene roxaparvovec are placeholder prices

Because the base case analysis of emicizumab found identical QALYs compared with factor VIII prophylaxis, it is not possible to calculate the usual threshold prices. In this situation, whichever therapy is less expensive (factor VIII was around 11% more expensive per year) would be preferred at all thresholds.

Table ES17 shows the threshold prices for valoctocogene roxaparvovec for the two SST shared cost-savings scenarios.

Table ES17. Threshold Analysis Results for the SST Shared Savings Scenarios in Model 1

Perspective	WAC per Unit	Net Price per Unit	Unit Price to Achieve $50,000 per QALY	Unit Price to Achieve $100,000 per QALY	Unit Price to Achieve $150,000 per QALY	Unit Price to Achieve $200,000 per QALY
Health Sector Half Cost Savings	$2,500,000	$2,500,000	$3,166,000	$3,166,000	$3,166,000	$3,166,000
Health Sector Capped Cost Savings ($150,000/yr)	$2,500,000	$2,500,000	$1,579,000	$1,581,000	$1,583,000	$1,585,000

WAC and net prices for valoctocogene roxaparvovec are placeholder prices

Summary and Comment

In this analysis of valoctocogene roxaparvovec, deemed preliminary due to issuance by the FDA of a complete response letter to its licensing application, and using a placeholder price of $2.5 million, the therapy was found to be a dominant treatment for adult patients with hemophilia A without inhibitors when using doses of factor VIII consistent with typical current practice in the US.

Given that valoctocogene roxaparvovec meets ICER's criteria to be considered a high-impact single and short-term therapy (SST), we performed additional scenario analyses including two shared savings scenarios. These shared savings scenarios result in a range of cost-effectiveness threshold prices between $1.6 million and $3.2 million, lower than the base case threshold prices of approximately $7.5 million. The purpose of producing these alternative scenarios is to provide empirical findings that may stimulate public dialogue on the extent to which large cost savings should be incorporated in judgments of reasonable pricing for novel therapies that are delivered as single or short-term interventions.

Using the average doses of factor VIII for prophylaxis as seen in the ATHN data set along with recent literature-based efficacy levels for factor VIII for patients in US hemophilia treatment centers that we believe represent evidence-based lower bounds on bleed rates for those treatments, emicizumab was found to be a highly cost saving treatment, with equal efficacy to factor VIII. In fact, model 2 using the base case doses for factor VIII would find emicizumab to be cost effective even if factor VIII were curative.

Overall, the findings illustrate that factor VIII is such an extremely costly treatment, especially at currently used dosages in the US, that new treatments are capable of generating large cost savings in comparison. If prices of factor VIII were to come down from effective competition or other measures, the appropriate pricing of new treatments, as suggested by cost-effectiveness thresholds, would come down significantly as well.

Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness.

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that was not available in the evidence base nor could be adequately estimated within the cost-effectiveness model. These elements are listed in the table below, with related information gathered from patients and other stakeholders. Following the public deliberation on this report the appraisal committee will vote on the degree to which each of these factors should affect overall judgments of long-term value for money of the intervention(s) in this review.

Valoctocogene Roxaparvovec

Table ES18.Categories of Potential Other Benefit and Contextual Considerations for Valoctocogene Roxaparvovec

Potential Other Benefit or Contextual Consideration	Relevant Information
Assumptions made in the base-case cost-effectiveness estimates rendering results overly optimistic or pessimistic.	
Whether the intervention represents a similar or novel mechanism of action compared to that of other active treatments.	If valoctocogene roxaparvovec had been approved, it would have been the first gene therapy for hemophilia A. It is unlike any other therapies for hemophilia A that are currently available.
Whether the delivery mechanism or relative complexity of the intervention under review is likely to very different real-world outcomes relative to an active comparator than estimated from clinical trials.	Administration of factor VIII prophylaxis is burdensome. Gene therapy with valoctocogene roxaparvovec is a one-time therapy after which adherence is not required. Adherence to gene therapy will be identical to that seen in clinical trials.
Whether the intervention will have a significant impact on the entire "infrastructure" of care, including patient screening, clinician sensitization, and condition awareness.	
Whether the intervention could reduce or preclude the potential effectiveness of future treatments.	Gene therapy with valoctocogene roxaparvovec induces antibodies to AAV5. It is unclear whether a patient who has received valoctocogene roxaparvovec can ever receive another AAV5-based gene therapy or be retreated with valoctocogene roxaparvovec.
Whether the intervention offers a special advantage for some patients by virtue of presenting an option with a notably different balance or timing of risks and benefits.	If valoctocogene roxaparvovec therapy is successful and generates several years of high levels of factor VIII, it could allow a patient to choose a period in life where they desire freedom from therapies for hemophilia. This could allow choices about education, career activities, travel, or sports that, though time-limited, might otherwise never be possible.
Whether the intervention differentially benefits a historically disadvantaged or underserved community.	Many patients with hemophilia who were alive in the late 1970s and early-through-mid 1980s were infected with HIV and died, and others were infected with hepatitis C and have now developed cirrhosis and its complications, further complicating their management of the condition. These infections were due to contamination of the medical therapies (factor replacement therapies) the patients were administered.
Whether there is a notably large or small health loss without this treatment as measured by absolute QALY shortfall.	Absolute QALY shortfall: 13.3 QALYs
Whether there is a notably large or small health loss without this treatment as measured by proportional QALY shortfall.	Proportional QALY shortfall: 0.26

Potential Other Benefit or Contextual Consideration	Relevant Information
Whether the intervention will significantly reduce the negative impact of the condition on family and caregivers vs. the comparator.	
Whether the intervention will have a significant impact on improving return to work and/or overall productivity vs. the comparator.	Valoctocogene roxaparvovec is likely to somewhat improve productivity of patients with hemophilia A.

Emicizumab

Table ES19. Categories of Potential Other Benefit and Contextual Considerations for Emicizumab

Potential Other Benefit or Contextual Consideration	Relevant Information
Assumptions made in the base-case cost-effectiveness estimates rendering results overly optimistic or pessimistic.	
Whether the intervention represents a similar or novel mechanism of action compared to that of other active treatments.	The mechanism of action of emicizumab is new for the treatment of patients with hemophilia A without inhibitors. As noted, it was initially introduced for the treatment of patients with hemophilia A with inhibitors.
Whether the delivery mechanism or relative complexity of the intervention under review is likely to very different real-world outcomes relative to an active comparator than estimated from clinical trials.	Administration of emicizumab is substantially easier than administration of factor VIII as it is given by subcutaneous injection rather than intravenous infusion making it easier and quicker to administer. It is also administered much less frequently than factor VIII. It is likely that this will improve adherence, result in some patients choosing prophylaxis who were previously only willing to use on-demand therapy, and somewhat enhance flexibility in choices around work, education, physical activity, and geographic mobility. Additionally, in infants and young children administration of factor VIII may require an implanted port that can result in complications such as infections and clotting. Adherence to emicizumab is likely to more closely approximate that seen in clinical trials than adherence to factor VIII prophylaxis.
Whether the intervention could reduce or preclude the potential effectiveness of future treatments.	
Whether the intervention offers a special advantage for some patients by virtue of presenting an option with a notably different balance or timing of risks and benefits.	

Potential Other Benefit or Contextual Consideration	Relevant Information
Whether the intervention differentially benefits a historically disadvantaged or underserved community.	Many patients with hemophilia who were alive in the late 1970s and early-through-mid 1980s were infected with HIV and died, and others were infected with hepatitis C and have now developed cirrhosis and its complications, further complicating their management of the condition. These infections were due to contamination of the medical therapies (factor replacement therapies) the patients were administered
Whether there is a notably large or small health loss without this treatment as measured by absolute QALY shortfall.	Absolute QALY shortfall: 13.3 QALYs
Whether there is a notably large or small health loss without this treatment as measured by proportional QALY shortfall.	Proportional QALY shortfall: 0.26
Whether the intervention will significantly reduce the negative impact of the condition on family and caregivers vs. the comparator.	Emicizumab is likely to reduce the burden on parents and caregivers of young children with hemophilia A.
Whether the intervention will have a significant impact on improving return to work and/or overall productivity vs. the comparator.	Emicizumab is likely to somewhat improve productivity of patients with hemophilia A.

Health Benefit Price Benchmarks and Potential Budget Impact

Given the FDA decision to issue a CRL for valoctocogene roxaparvovec, ICER is not presenting health benefit price benchmarks (HBPBs) or a potential budget impact analysis for valoctocogene roxaparvovec.

Health benefit price benchmarks for the population of hemophilia patients without inhibitors were also not calculated for emicizumab, as treatment at the current price compared with factor VIII is projected to be cost saving and produce at least as many QALYs. Additionally, unless indication-specific pricing occurred, the HBPB for emicizumab should include its use in patients with inhibitors. As emicizumab already has an established presence in the market, no potential budget impact analysis is included for emicizumab.

New England CEPAC Votes

The New England CEPAC deliberated on key questions raised by ICER's report at a public meeting on October 30, 2020. The results of these votes are presented below, and additional information on the deliberation surrounding the votes can be found in the full report.

1) For patients with hemophilia A without inhibitors to factor VIII, is the evidence adequate to demonstrate that the net health benefit of **emicizumab** (Hemlibra, Genentech) is superior to that provided by prophylaxis with factor VIII?

Yes: 15 votes	No: 0 votes

2) Please vote 1, 2, or 3 on the following potential other benefits and contextual considerations as they relate to **emicizumab**.

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
Uncertainty or overly favorable model assumptions creates significant risk that base-case cost-effectiveness estimates are too optimistic.		Uncertainty or overly unfavorable model assumptions creates significant risk that base-case cost-effectiveness estimates are too pessimistic.
	10 votes	5 votes

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
Very similar mechanism of action to that of other active treatments.		New mechanism of action compared to that of other active treatments.
		15 votes

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
Delivery mechanism or relative complexity of regimen likely to lead to much lower real-world adherence and worse outcomes relative to an active comparator than estimated from clinical trials.		Delivery mechanism or relative simplicity of regimen likely to result in much higher real-world adherence and better outcomes relative to an active comparator than estimated from clinical trials.
		15 votes

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
This intervention could reduce or preclude the potential effectiveness of future treatments.		This intervention offers the potential to increase access to future treatment that may be approved over the course of a patient's lifetime.
	15 votes	

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
The intervention offers no special advantages to patients by virtue of presenting an option with a notably different balance or timing of risks and benefits.		The intervention offers special advantages to patients by virtue of presenting an option with a notably different balance or timing of risks and benefits.
3 votes	**9 votes**	3 votes

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
This intervention will not differentially benefit a historically disadvantaged or underserved community.		This intervention will differentially benefit a historically disadvantaged or underserved community.
	3 votes	**12 votes**

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
Small health loss without this treatment as measured by absolute QALY shortfall.		Substantial health loss without this treatment as measured by absolute QALY shortfall.
1 vote	**8 votes**	6 votes

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
Small health loss without this treatment as measured by proportional QALY shortfall.		Substantial health loss without this treatment as measured by proportional QALY shortfall.
3 votes	**10 votes**	2 votes

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
Will not significantly reduce the negative impact of the condition on family and caregivers vs. the comparator.		Will significantly reduce the negative impact of the condition on family and caregivers vs. the comparator.
		15 votes

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
Will not have a significant impact on improving return to work and/or overall productivity vs. the comparator.		Will have a significant impact on improving return to work and/or overall productivity vs. the comparator.
	1 vote	**14 votes**

Key Policy Implications

Following its deliberation on the evidence, the New England CEPAC engaged in a moderated discussion with a policy roundtable about how best to apply the evidence on emicizumab and valoctocogene roxaparvovec to policy and practice of hemophilia A care. The policy roundtable members included 2 patient experts, 2 clinical experts, 2 payer representatives, and 3 representatives from pharmaceutical manufacturers. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. The top-line policy implications are presented below, and additional information can be found in the full report.

Manufacturers

- Pricing of factor VIII represents a failure of competition and is far too high, even in light of factor VIII's substantial benefits for patients; this pricing structure creates financial toxicity for patients and their families, financial toxicity for health systems, and builds a platform for pricing for potential cures that will only exacerbate these problems.
- In order to facilitate broad access to the current standard for clinically superior care, both in the US and abroad, drug makers should commit to pricing factor VIII so that the cost to achieve trough levels of 3-5% is the same or lower than what it cost in the past to achieve a 1% trough level.
- Manufacturers and Researchers should ensure that clinical trials capture a core set of outcomes that are important to patients.
- Trials of gene therapies for hemophilia need to be long enough to assess whether the benefits are durable enough to outweigh the risks, particularly since patients may be unlikely to be able to receive a second gene therapy using the same viral vector.
- Manufacturers and researchers should study the effects of emicizumab on the development of inhibitors in infancy and early childhood.

Payers

- Payers should cover factor VIII prophylaxis at levels adequate to achieve higher troughs than the 1% level used in the past.
- Considering the evidence of equivalent to improved comparative effectiveness, relative convenience, and lower overall cost, emicizumab will be the preferred agent for prophylaxis for many patients. Payers should ensure appropriate access to emicizumab and may wish to share information with clinicians and patients regarding its potential advantages over factor VIII prophylaxis.
- Payers may wish to require that management of factor VIII be done by or in consultation with a Hemophilia Treatment Center.
- Payers should explore innovative approaches to covering high-impact single time therapies such as gene therapies for hemophilia.

Patient Advocacy Organizations

- Patient groups should fully embrace their power to speak explicitly about the impact of the high prices of treatments for hemophilia A. General statements of concern about "costs" shifts the focus subtly away from prices, which is consistent with the interests of the life science industry. Doing so deflects from the reality that drug makers have the power to set prices in the United States and the result produces affordability concerns for health systems, financial toxicity for patients and families, and barriers to the ability of patients to

gain access to optimal clinical care. Hemophilia patient groups should be willing to name the problem and bear witness to the harms that excessive prices cause.

- Patient groups should be fully transparent about the sources and levels of their funding from industry sources.

Regulators

- Regulators should require manufacturers of expensive therapies such as those for hemophilia A to provide packaging that minimizes wastage.

All Stakeholders and Policy Makers

- It is counterintuitive to pay more for new treatments simply because the existing treatments are overpriced.

1. Introduction

1.1 Background

Background

ICER reviewed emicizumab for hemophilia A in patients with factor VIII inhibitors in 2018 (Emicizumab for Hemophilia A with Inhibitors: Effectiveness and Value). Much of the background information in this report is reproduced from that report.

Hemophilia A is a condition of increased tendency to bleed due to an inherited deficiency of factor VIII, which disrupts the clotting cascade (Figure 1). Hemophilia A has X-linked recessive inheritance, and so predominately affects males. It is the most common of the hemophilias with an incidence of one in 5,000 male births.[1] The exact prevalence of hemophilia in the United States (US) is not known, but is estimated to be around 20,000.[46] Approximately 77% of all hemophilia patients in the US have hemophilia A.[47]

Patients with hemophilia A, particularly those with severe disease, are at risk for life-threatening bleeding, including intracranial bleeding, but bleeding into a joint (hemarthrosis) or muscle is more common and can lead to substantial disability.[2] Hemarthroses cause ongoing joint inflammation and damage and also increase the likelihood of further bleeding into the same joint.

Severity of hemophilia A has generally been defined by factor levels (the percentage of normal factor that a patient has).[17] However, severity based on factor levels does not perfectly correlate with actual clinical severity.[48] Despite this, other severity classifications are not yet widely accepted, and factor levels define severity in most clinical trials. Using factor level classifications, severe disease is defined by factor VIII levels below 1% of normal.[17] Patients with severe disease who are not receiving prophylactic treatment experience an average of 20 to 30 episodes of spontaneous bleeding or excessive bleeding after minor trauma per year.[1] Patients with moderate disease (factor VIII levels of 1% to 5% of normal) typically have delayed bleeding episodes after minor trauma several times per year, but only occasionally have spontaneous bleeding.[3] Individuals with mild disease (factor VIII levels between 6% to 40% of normal) typically have bleeding after procedures such as tooth extractions or surgery, or after significant injuries.

To reduce the risk of bleeding, patients with severe hemophilia A have typically administered factor VIII concentrate intravenously multiple times per week.[3,4] The use of factor concentrates both as treatment and prophylaxis has dramatically altered the management and clinical course of patients with hemophilia A. However, prophylaxis with factor replacement is burdensome and does not maintain patients at normal levels of factor VIII. A number of factor VIII preparations are available

for prophylaxis, some with modifications to extend the half-life of the therapy, some prepared from human plasma, and some prepared using recombinant technology.

Unfortunately, along with the advances in treatment of hemophilia A and B, the products used in the 1970s and 1980s were contaminated with viruses; of particular importance, HIV and hepatitis C (widespread hepatitis B testing of donor blood used to manufacture blood products occurred by 1975 and hepatitis B vaccine, developed in the 1980s, provided further protection from HBV transmission via blood products). Although by the mid-1980s testing for antibodies to HIV and treatment of donor blood used to manufacture blood products dramatically improved the safety of these products, people with hemophilia treated prior to this time were very likely to develop infection. AIDS resulted in the deaths of thousands of patients with hemophilia A before effective treatment became available in the late 1990s.[49] Hepatitis C, a more indolent virus, led to cirrhosis and death in many additional patients, and only in recent years has a highly effective and tolerable treatment for hepatitis C been developed.

Administration of Factor VIII

Factor VIII concentrate is given intravenously, whether administered on-demand or prophylactically. Prophylaxis is administered multiple times per week, which is burdensome.[5]

Intravenous access requires skill and can be difficult to master and painful, and over many years of treatment accessible veins may clot and no longer be useable. If patients develop arthropathy of upper extremity joints from hemarthroses or become infirm as they age, self-administration of factor concentrate may be more difficult or impossible.

Young children may present particular problems for venous access, both because of an inability to cooperate and because of small veins. For this reason, implanted venous access devices are frequently required for young children. These devices, which include a port placed below the skin, can clot and can become infected, which typically requires hospitalization to receive intravenous antibiotics and/or to replace the device. Even with such devices, it is generally impractical to initiate prophylaxis until late in the first year of life.

Not surprisingly, adherence to an intravenous therapy that must be administered frequently can be difficult for patients who are appropriate candidates for prophylaxis. Only 50%-70% of patients adhere to prophylaxis regimens, particularly once they are old enough to make treatment decisions for themselves.[6,7]

Emicizumab

Emicizumab-kxwh (Hemlibra®, Genentech, referred to as "emicizumab" in this Report) is a monoclonal antibody with dual targets ("bispecific") that allow it to bridge activated factor IX and factor X, the role normally played by activated factor VIII in the clotting cascade (Figure 1).[8] Emicizumab was approved by the US Food and Drug Administration (FDA) as a prophylactic treatment for hemophilia A in patients who have inhibitors to factor VIII in 2017 and in those without inhibitors in 2018.[9] Emicizumab is administered subcutaneously and may be dosed weekly, every two weeks, or every four weeks based on provider and patient preference.

Patients without inhibitors who require treatment for bleeding while receiving emicizumab will generally be treated with a factor VIII preparation as on-demand therapy.

Prior to the approval of emicizumab, patients who developed inhibitors to factor VIII that could not be eradicated required bypassing agents such as activated prothrombin complex concentrate or recombinant activated factor VIII administered frequently and at high cost for prophylaxis.[50-52] Patients with inhibitors who require treatment for bleeding while receiving emicizumab will generally be treated with a bypassing agent as on-demand therapy and treatment of a single bleeding episode can cost $50,000 or more.[51,52] ICER found in 2018 that in patients with factor inhibitors, prophylaxis with emicizumab was cost saving (Emicizumab for Hemophilia A with Inhibitors: Effectiveness and Value), even though the wholesale acquisition cost (WAC) of emicizumab was approximately $482,000 for the first year of treatment and $448,000 for subsequent years at the time. Patients with factor inhibitors are not included in this current review.

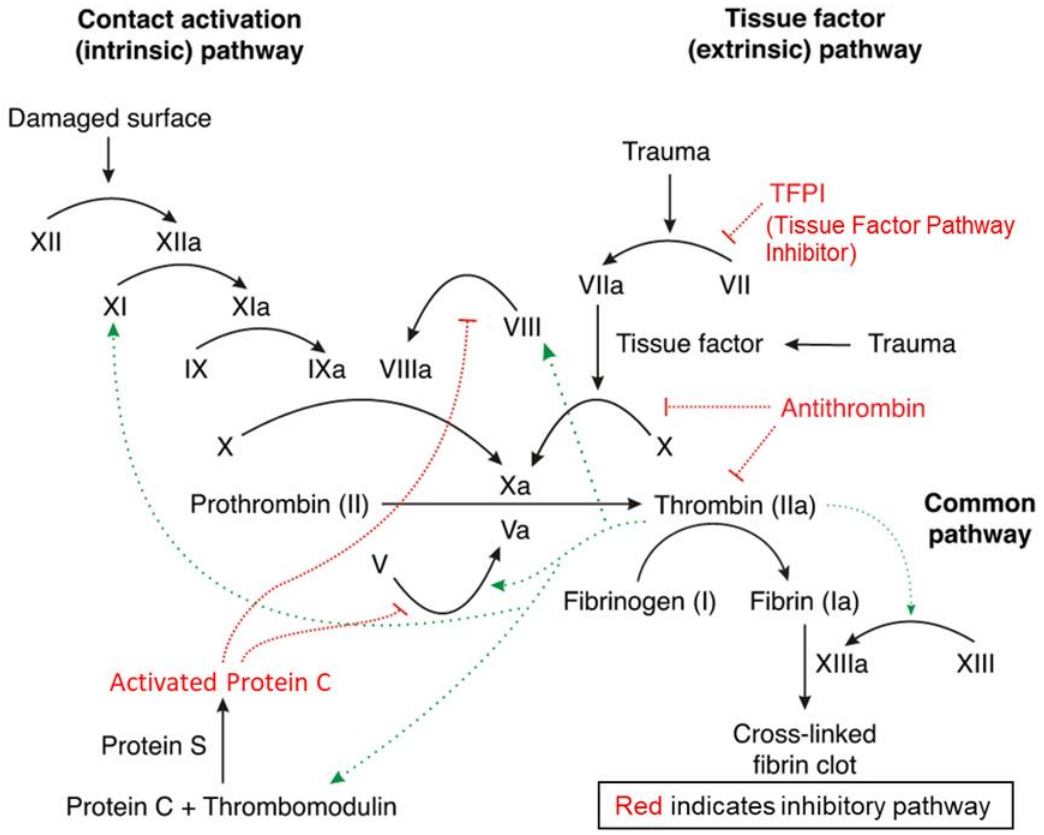
Valoctocogene Roxaparvovec

Valoctocogene roxaparvovec (Roctavian; BioMarin) is an adeno-associated virus serotype 5 (AAV5) mediated liver-directed gene therapy for hemophilia A.[10] Gene therapy for hemophilia A is difficult because of the size of the factor VIII gene. The complete gene is too large to fit into an AAV capsid. Valoctocogene roxaparvovec delivers a B-domain-deleted factor VIII gene with a liver-specific transcription promotor as a mixture of 5' or 3' incomplete strands in each capsid that must then anneal to form the full length B-domain-deleted gene required for production of factor VIII.[10,13] Although liver production of factor VIII normally occurs in liver sinusoid endothelial cells, the target of valoctocogene roxaparvovec is hepatocytes.[11] Thus gene therapy with valoctocogene roxaparvovec results in factor VIII production in the liver, but not in the cells in the liver that normally produce factor VIII.

Published information is available on a limited number of patients who received therapy with valoctocogene roxaparvovec, with up to three years of follow-up. Public presentations have some information after four years of follow-up and on a subset of patients in a phase III trial of valoctocogene roxaparvovec.

BioMarin submitted a biologics license application for valoctocogene roxaparvovec to the FDA in December 2019 and received a Complete Response Letter (CRL) rejecting approval in August 2020.[12] As a result of this FDA decision and the expectation that two years of additional data on valoctocogene roxaparvovec will be available prior to future FDA consideration for approval, ICER considers all results in this report related to valoctocogene roxaparvovec, including results on comparative effectiveness and cost effectiveness, to be highly preliminary. ICER will not be suggesting health benefit price benchmarks for valoctocogene roxaparvovec nor will analyses be performed to evaluate potential budget impact. Nonetheless, ICER believes that it is in patients' and the public interest to publish the preliminary findings of the review to support future discussions and decisions regarding how best to generate and assess evidence on the clinical and cost-effectiveness of valoctocogene roxaparvovec.

Figure 1.1. Illustration of Activated Factor VIII in the Clotting Cascade



Source: Joe Dunckley, own work. Adapted with permission under the conditions of CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=1983833.

1.2 Scope of the Assessment

The scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence was sought from

randomized controlled trials as well as high-quality systematic reviews; observational studies and case series were considered for inclusion as well, given the limited evidence base for valoctocogene roxaparvovec.

Populations

The population of focus for this review is people with hemophilia A without inhibitors to factor VIII who would be appropriate for routine prophylaxis with factor VIII. For valoctocogene roxaparvovec, we limited the review to an adult population.

Interventions

The interventions of interest for this review are listed below:

- Valoctocogene roxaparvovec
- Emicizumab

Comparators

We compared the interventions to each other and to prophylaxis with factor VIII preparations.

Outcomes

We looked for evidence on the following outcomes of interest:

- Patient Important Outcomes:
    - Patient-reported quality of life
    - Rates of bleeding events
    - Rates of treated bleeding events
    - Rates of treated joint bleeding and treated target joint bleeding
    - Pain (chronic and acute)
    - Mental health status
    - Burdens of therapy
    - Mortality
    - Adverse events including:
        - Thrombosis
        - Liver toxicity

- Other outcomes:
    - Factor level (factor activity level)
    - Duration of expression of the clotting factor gene
    - Utilization of health care system

- Adverse events including:
    - Immune response to FVIII (Inhibitor development)
    - Immune response to gene therapy

We also looked for evidence on additional patient-reported outcomes, such as employment, disability status, social engagement, overall well-being, mobility (activity), anxiety, and depression, as available, as well as outcomes for family and caregivers, particularly for younger children with hemophilia A.

Timing

Evidence on intervention effectiveness was derived from studies of any duration.

Settings

Evidence from all relevant settings was considered, including inpatient, outpatient/clinic, office, and home settings.

1.3 Definitions

Target Joint: This term is used to describe a joint that has had recurrent bleeding. The exact definition varies, but it is commonly defined as a joint that has had three or more spontaneous bleeds within a consecutive six-month period.[17]

Arthropathy: A disease of a joint. In patients with hemophilia, bleeding into a joint (hemarthrosis) causes injury and inflammation which can cause permanent damage to the joint.

Pettersson Score: A validated radiological scoring system that is used to estimate the level of joint destruction. It is widely used to classify the osteochondral changes of hemophilic arthropathy in elbows, knees, and ankles.[53]

Hemophilia Quality of Life Index for Adults (Haem-A-QoL): A hemophilia-specific, validated, 46-item instrument used to assess the health-related quality of life in adult patients. It is based on a total score transformed to a scale of 0 to 100, with lower scores reflecting better health-related quality of life.[54]

Hemophilia-specific quality of life questionnaire for adults (Haemo-Qol-A): A hemophilia-specific, validated 41-item instrument that evaluates six health-related quality of life domains in adult patients: physical functioning, role functioning, worry, bleeding consequences, emotional impact, and treatment concerns. It is based on a total score transformed to a scale of 0 (worst) to 100 (best).[55]

Patient Reported Outcomes, Burdens and Experiences (PROBE) questionnaire: A hemophilia-specific, validated questionnaire that that evaluates three domains: general health problems (e.g., use of pain medication, limitation in mobility, and absence from school or work), hemophilia specific problems (e.g., presence of target joints, number of bleeds in the past 12 months), and health-related quality of life (using the EuroQol five dimension 5-level instrument [EQ-5D-5L] and the EuroQol visual analogue scale [EQ-VAS] of global health tools).[20]

1.4 Research, Development, and Manufacturing Costs

As described in ICER's modified framework for assessing value of treatments for ultra-rare diseases, ICER invited manufacturers to submit relevant information on research, development, and manufacturing costs that may impact pricing of a drug. For this report, no manufacturer submitted information on development or production costs that they believed would be an important factor in justifying the price of their product.

1.5 Potential Cost-Saving Measures in Hemophilia A

As described in its Value Assessment Framework for 2020-2023, ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/wp-content/uploads/2019/05/ICER_2020_2023_VAF_013120-2.pdf). These services are not ones that would be directly affected by gene therapy or emicizumab (e.g., fewer bleeds), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of hemophilia beyond the potential offsets that arise from a new intervention. We received no suggestions.

2. Patient Perspectives

2.1 Methods

During ICER's scoping, open input, and public comment periods, we received public comment submissions from 13 stakeholders (4 patient advocacy groups, 6 manufacturers, and 3 multi-stakeholder group) and participated in conversations with 11 key informants (3 patients, 2 patient advocacy groups, 3 manufacturers, and 5 clinical experts). Some stakeholders played more than one role in our outreach. These comments and conversations, along with ICER's 2018 report on emicizumab for hemophilia A, helped us to discuss the impact on patients as described below.

2.2 Impact on Patients

We heard from patients and patient groups that hemophilia can restrict:

- Career choices for the patient and caregivers
- Educational choices for the patient
- Decisions about where to live for the patient and caregivers
- Recreational activities
- Family structure (marriage, divorce, etc.) and employment choices because of concerns about the need to maintain insurance

These generally relate to issues of bleeding risk, being near specialized care, having factor replacement therapy quickly accessible, and having flexible time to deal with bleeding events that can affect choices of both patients and caregivers (Table 2.1). Over time, joint injury from bleeding can further restrict patient activities due to pain and inflammation, and in some cases, may require joint replacement surgery. These same joint injuries can eventually limit the ability of patients to care for themselves, as arthritis caused by bleeds may prevent patients from self-administering intravenous infusions.

People with hemophilia may be unable to enter their career of choice; professions that involve manual labor (e.g., farming, carpentry, construction) may involve too great a risk of bleeding. Even people who are employed in professions that do not carry large bleeding risks must ensure that their work keeps them in the proximity of a medical center that is able to provide urgent/emergent treatment.

There is a substantial time burden associated with prophylaxis with factor VIII, as patients who require multiple doses per week must find time for infusions; this can be particularly challenging for caregivers of young and school-aged children, as infusion would need to take place before the school day, and the parent/caregiver's work day, begins. Caregivers of patients who receive

infusions through a port must also carefully monitor the port for infection, and such devices may also need to be periodically replaced, and, if they become infected, may require hospitalization for antibiotic treatment, adding to financial and time burdens.

Traditional day care centers are unlikely to be adequately equipped to care for a young child with hemophilia, complicating childcare choices for parents and caregivers. Children may also not be able to participate in common social activities, such as birthday parties, for fear of an accident that causes a bleed.

Table 2.1. Reasons for Potential Patient and Caregiver Restrictions Related to Hemophilia A

	Bleeding Risk	Near Specialized Care	Accessibility of Factor	Flexible Time
Caregiver Career		×		×
Patient Career	×	×	×	×
Education		×	×	×
Location of Residence		×	×	
Recreation	×	×	×	

On the issue of a potentially curative therapy for hemophilia, we heard from a patient whose hemophilia was cured by liver transplantation. He noted that this transformed his life in a way that he did not feel he could have completely understood prior to the transplantation and that there was a level of value in this transformation not adequately captured by existing outcome sets for patients with hemophilia.

In response to the Draft Evidence Report, we heard concerns from patients and patient groups that they had struggled to get insurance coverage for dosing regimens of factor VIII that maintain trough levels high enough to adequately control risk of bleeding.

3. Summary of Coverage Policies and Clinical Guidelines

3.1 Coverage Policies

We reviewed the Tufts Medical Center Specialty Drug Evidence and Coverage (SPEC) Database for its US commercial health plans' coverage policies for emicizumab (HEMLIBRA®, Genentech), current as of April 2020.[56] Developed by the Center for Evaluation of Value and Risk in Health, the SPEC database features data on more than 290 specialty drugs, more than 175 disease areas, and more than 25,000 decisions from the following 17 largest US national and regional commercial payers: Aetna, Anthem, Blue Cross Blue Shield (BCBS) of Florida (FL), Massachusetts (MA), Michigan (MI), North Carolina (NC), New Jersey (NJ), and Tennessee (TN), CareFirst, Centene, Cigna, Emblem, Health Care Service Corporation (HCSC), Highmark, Humana, Independence Blue Cross (IndepBC), and UnitedHealthcare (UHC).

On August 18, 2020, the FDA issued a Complete Response Letter to BioMarin's Biologic License Application for valoctocogene roxaparvovec, precluding a survey of its coverage policies.[12]

Emicizumab

Of the 17 payers surveyed through the SPEC database, 15 (88%) had publicly-available coverage policies for emicizumab; BCBSMA and BCBSTN did not have policies available (Table 3.1). Compared to the FDA labeled indication for emicizumab, 12 (80%) of the 15 payers had more restrictive coverage criteria while Aetna, CareFirst, and HCSC had equivalent coverage. Patient subgroup restrictions involved severity of hemophilia, presence of inhibitors, documented history of specified bleed types, and factor VIII levels. For prescriber restrictions, Centene and IndepBC required that emicizumab be prescribed in consultation with a hematologist, while BCBSMI and BCBSNC required consultation with a specialist in hemophilia. Of the 15 payers who cover emicizumab, 9 (60%) cover emicizumab as first line therapy for hemophilia A (Table 3.1). The remaining payers – BCBSMI, BCBSNC, BCBSNJ, Centene, Humana, and UHC – require a stepwise protocol with criteria ranging from ineffective prophylaxis with factor VIII treatment, intolerance or contraindication to factor VIII treatment, spontaneous or breakthrough bleeding, failure of prophylaxis with bypassing agents, failure of immunosuppressants or corticosteroids to lower antibody levels, or failure of immune tolerance induction (ITI).

Table 3.1. Representative Private Payer Policies for Emicizumab

Payer	Covered?	Coverage Restrictiveness vs. FDA Label Indication	Patient Subgroup Restriction (Clinical Criteria)?	Step Therapy Protocol?	Prescriber Requirement
Aetna	Yes	Equivalent	No	No	No
Anthem	Yes	More Restrictive	Yes	No	No
BCBSFL	Yes	More Restrictive	Yes	No	No
BCBSMA	No policy	No policy	No policy	No policy	No policy
BCBSMI	Yes	More Restrictive	Yes	Yes	Yes
BCBSNC	Yes	More Restrictive	Yes	Yes	Yes
BCBSNJ	Yes	More Restrictive	Yes	Yes	No
BCBSTN	No policy	No policy	No policy	No policy	No policy
CareFirst	Yes	Equivalent	No	No	No
Centene	Yes	More Restrictive	Yes	Yes	Yes
Cigna	Yes	More Restrictive	Yes	No	No
Emblem	Yes	More Restrictive	Yes	No	No
HCSC	Yes	Equivalent	No	No	No
Highmark	Yes	More Restrictive	Yes	No	No
Humana	Yes	More Restrictive	Yes	Yes	No
IndepBC	Yes	More Restrictive	No	No	Yes
United	Yes	More Restrictive	Yes	Yes	No

FDA: Food and Drug Administration

3.2 Clinical Guidelines

National Hemophilia Foundation, Medical and Scientific Advisory Council (MASAC) Recommendations, Recommendation on the Use and Management of Emicizumab-kxwh (Hemlibra®) for Hemophilia A with and without Inhibitors, March 2020[57]

The MASAC guidelines indicate routine prophylaxis with emicizumab for adults and children of all ages, including newborns, with hemophilia A with and without factor VIII inhibitors. Due to the increased risk of intracranial hemorrhage prior to initiation of FVIII prophylaxis, infants should be considered for prophylaxis with emicizumab at any time after birth. Although the clinical trial data on the use of emicizumab in infants under 6 months of age is limited, the published evidence still supports prophylactic efficacy of emicizumab in infants.

In the event of breakthrough bleeding while on emicizumab prophylaxis, all standard half-life and extended half-life FVIII concentrates are acceptable for concomitant use, following the dosing recommendations for FVIII replacement therapy.

World Federation of Hemophilia, Guidelines for the Management of Hemophilia, 3rd Edition, August 2020[58]

The World Federation of Hemophilia's 2020 Guidelines strongly recommend that patients with a severe phenotype of hemophilia A be on prophylaxis sufficient to prevent all bleeds. Especially among children, long-term prophylaxis is indicated as the standard of care to prevent bleeding, hemarthrosis, and to promote quality of life. Based on bleeding phenotype, individual pharmacokinetics, and joint status, the prophylactic regimen should be tailored to the individual patient when possible.

WFH recommends early initiation of prophylaxis (before age 3 and before onset of joint disease) with clotting factor for pediatric patients with severe hemophilia A. Dosing and dosing interval for prophylaxis with clotting factor (either standard or extended half-life) should be sufficient to prevent spontaneous and breakthrough bleeding, and hemarthrosis. In the event of breakthrough bleeds even while on a prophylactic regimen, the WFH recommends escalation of prophylactic dose and orthopedic interventions, as necessary.

For patients with severe phenotype hemophilia A without inhibitors, prophylaxis with emicizumab will prevent hemarthrosis, spontaneous, and breakthrough bleeding. The initiation of emicizumab in newborns has not been well studied, and the data are limited regarding whether emicizumab may be initiated earlier than clotting factor concentrates.

British Society for Haematology, Guidelines on the Use of Prophylactic Factor Replacement for Children and Adults with Haemophilia A and B, May 2020[59]

The 2020 guidelines released by the British Society for Haematology (BSH) recommends lifelong prophylaxis as the standard of care for hemophilia therapy. Prophylaxis is advised for any person with hemophilia who sustains at least one spontaneous joint bleed or has established joint damage due to hemarthrosis.

For any person with severe hemophilia or moderate hemophilia with a baseline factor level between 1-3 IU/dl, primary prophylaxis is recommended before or immediately following the first joint bleed. Similarly, primary prophylaxis is also recommended for all children with severe hemophilia A or with baseline factor levels between 1-3 IU/dl.

Shared decision-making between children with hemophilia and their legal guardian is recommended when choosing the factor replacement product. Extended half-life recombinant FVIII is only advised when it presents a clear clinical benefit over the standard half-life products.

Emicizumab is recommended as an alternative to FVIII prophylaxis for persons with severe hemophilia A older than 2 years and without inhibitors. Due to the paucity of data for severe hemophilia A patients who are less than 2 years old, with or without inhibitors, BSH cautions against the use of emicizumab in this population.

Home therapy can allow prompt access to clotting factor and therefore offers improved outcomes (e.g., decreased pain, dysfunction, disability) and reduces complications resulting in hospital admissions. A home therapy setting is only appropriate after adequate training and should employ close monitoring from a comprehensive care team.

European Directorate for the Quality of Medicine and Healthcare – A Council of Europe Body, 2019[60]

Patients with severe hemophilia experience persistent and prolonged spontaneous bleeding episodes, primarily in muscles and joints, that result in disabling musculoskeletal damage and chronic arthropathy. Prophylaxis in hemophilia is aimed at reducing the risk of bleeding in order to preserve normal musculoskeletal function. With the advent of extended half-life therapies, the European Directorate for the Quality of Medicine and Healthcare (EDQM) recommends achieving a minimum trough level of 3-5% to preserve joint status. Prophylaxis dosing regimens using standard half-life FVIII and FIX products can produce trough plasma levels of 1-2%, but the introduction of extended half-life products significantly improves efficacy by achieving higher trough levels.

4. Comparative Clinical Effectiveness

4.1 Overview

To inform our review of the comparative clinical effectiveness of valoctocogene roxaparvovec gene therapy and emicizumab in the treatment of hemophilia A without factor VIII inhibitors, we systematically identified and synthesized the existing evidence from available clinical studies. Our review focused on clinical benefits, as well as potential harms (treatment-related adverse events) of these agents compared to each other and to factor VIII prophylaxis. We sought evidence on all outcomes listed in Section 1.2. Because valoctocogene roxaparvovec was studied only in adults, we limited our review of this intervention to the adult population. Methods and findings of our review of the clinical evidence are described in the sections that follow.

4.2 Methods

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on new therapies for hemophilia A without factor VIII inhibitors followed established best research methods.[61,62] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[63] The PRISMA guidelines include a checklist of 27 items, which are described further in Appendix Table A1.

We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design elements described in Section 1.2. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms (see Appendix Table A2).

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework-2/grey-literature-policy/). Where feasible and deemed necessary, we also accepted data submitted by

manufacturers "in-confidence," in accordance with ICER's published guidelines on acceptance and use of such data (https://icer-review.org/use-of-in-confidence-data/).

Study Selection

We included evidence on valoctocogene roxaparvovec and emicizumab from all relevant published clinical studies irrespective of whether they used a comparative study design. With respect to factor VIII prophylaxis, studies were included if they compared factor VIII prophylaxis to on-demand treatment. We excluded studies conducted in patients with acquired hemophilia, and in patients with hemophilia A and factor VIII inhibitors.

In recognition of the evolving evidence base for hemophilia A, we also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see http://icer-review.org/methodology/icersmethods/icer-value-assessment-framework/grey-literature-policy/). We excluded abstracts which reported duplicative data available in published articles.

Data Extraction and Quality Assessment

Two reviewers extracted key information from the full set of accepted studies. We used criteria employed by the US Preventive Services Task Force (USPSTF) to assess the quality of clinical trials. For more information on data extraction and quality assessment, see Appendix D.

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus (see Appendix D).[64,65]

Data Synthesis and Statistical Analyses

Data on relevant outcomes were summarized in evidence tables (see Appendix Tables D1 and D2) and synthesized quantitatively and qualitatively in the body of the review. Based on the availability of data from sufficiently similar trials, network meta-analyses (NMAs) were conducted to compare emicizumab with factor VIII prophylaxis on the following outcomes of interest: rates of treated bleeding events and rates of treated joint bleeding. Due to major differences in study design and study characteristics, we did not conduct NMAs to compare valoctocogene roxaparvovec to emicizumab or factor VIII prophylaxis. All NMAs were conducted in a Bayesian framework with random effects on the treatment parameters using the gemtc package in R.[66] The outcomes analyzed were all rate ratios and were analyzed using a Poisson likelihood and the log link function.

Further information on the NMA, including decisions around NMA feasibility and methods are presented are presented in Appendix D.

4.3 Results

Study Selection

Our literature search identified 1158 potentially relevant references (see Appendix Figure A1), of which 16 references met our inclusion criteria. Primary reasons for study exclusion included study populations outside of our scope, reporting of outcomes not relevant to this review, and conference abstracts or posters reporting data subsequently published in peer-reviewed literature.

Of the 16 references, five of the references (2 publications, 2 conference presentations, and 1 press release)[10,13-16] corresponded to two non-randomized trials of valoctocogene roxaparvovec gene therapy (one Phase I/II and one Phase III).

Six references (3 publications and 3 conference abstracts)[21-26] corresponded to three unique Phase III trials (1 randomized and 2 non-randomized) of emicizumab.

In addition, we identified five references corresponding to four factor VIII trials that could potentially inform an indirect comparison of factor VIII prophylaxis to emicizumab.[27,28,67-69] Following further evaluation of these trials, only one (SPINART) was found to be sufficiently similar to the randomized trial of emicizumab in terms of baseline characteristics, study design and outcome definition to permit NMA.[27,28] Reasons for excluding the other three randomized trials of factor VIII prophylaxis are presented in Appendix Tables D3 and D4.

Full details of all studies included in our systematic literature review are provided in Appendix D. Key trial details including participant characteristics and clinical benefits are presented below.

Quality of Individual Studies

We rated the two RCTs in our study set (1 emicizumab trial [HAVEN 3] & 1 factor VIII trial [SPINART]) to be of good quality using criteria from the USPSTF (Appendix D). Additional details for each trial regarding the comparability of groups, participant blinding, validity of outcome assessments, intervention definitions, and key outcome reporting can be found in Appendix D. The four other studies in our set were non-randomized and lacked a placebo or active control group, thus we did not assign any quality rating to these trials. The limitations, uncertainties, and gaps in evidence of these trials are discussed in the Controversies and Uncertainties section.

Assessment of Publication Bias

As described in our methods, we searched for studies completed more than two years ago which would have met our inclusion criteria, and for which no findings have been published. Any such studies may have provided qualitative evidence for the presence of potential publication bias. Given the emerging nature of the evidence base for newer treatments, we performed an assessment of publication bias for valoctocogene roxaparvovec and emicizumab using the clinicaltrials.gov database of trials. For this review, we did not find evidence of any study completed more than two years ago that that has not subsequently been published. We note, however, that limited topline interim (26-week) results from the Phase III GENEr8-1 trial of valoctocogene roxaparvovec were released by the manufacturer in May 2019 and those results have not been published in detail and no additional interim results have been released.

Trials of Valoctocogene Roxaparvovec

We identified two trials of valoctocogene roxaparvovec (one Phase I/II and one Phase III) that met our inclusion criteria, neither of which had a control arm (Table 4.1).

Key Trial of Valoctocogene Roxaparvovec

Phase I/II Trial (NCT02576795)

Evidence to inform our assessment of valoctocogene roxaparvovec were mainly derived from an open-label dose-escalation Phase I/II multiyear study conducted in 15 patients.[10,13,14,18,19] The trial enrolled male patients aged 18 years and older with severe hemophilia A without factor VIII inhibitors who had at least 150 days of previous exposure to factor VIII concentrate or cryoprecipitate. For patients who were receiving on-demand treatment, they had to have at least 12 bleeding events requiring factor VIII replacement treatment in the previous 12 months. Patients with pre-existing immunity to the adeno-associated virus type 5 (AAV5) capsid or those who showed any evidence of active infection or immunosuppressive disorder or tested positive for HIV were excluded.

Fifteen eligible patients were assigned to one of four cohorts, and given a single intravenous infusion of valoctocogene roxaparvovec at varying doses: cohort 1 ($6x10^{12}$ vector genomes [vg]/kg dose; n=1), cohort 2 ($2 x10^{13}$ vg/kg dose; n=1), cohort 3 ($6x10^{13}$ vg/kg dose; n=7) or cohort 4 ($4x10^{13}$ vg/kg dose; n=6). The alanine aminotransferase level reached 1.5 times the baseline value in the first participant in cohort 3, consequently, the remaining six participants in the cohort received a therapeutic course of prophylactic glucocorticoids as required by the protocol. However, a protocol amendment later removed the requirement for glucocorticoid prophylaxis, so participants in cohort 4 were treated with glucocorticoids as needed. Factor VIII prophylaxis was stopped in all patients; however, patients could administer factor VIII as needed for breakthrough bleeding events.

The median age of patients in the trial was 30 years (range: 23-42 years). At baseline, all participants had been on factor VIII prophylaxis except for one participant in cohort 3 who was receiving on-demand factor VIII. The mean annualized rate of bleeding events among patients who were on prophylaxis was 14 (range: 0-41). The baseline bleeding rate was not reported for the one patient who was receiving on-demand treatment.

The primary efficacy outcome was achievement of factor VIII activity level of 5 IU/dL at week 16 after gene transfer. Five-year assessment of safety events was a co-primary endpoint. Other outcomes of interest included yearly evaluation of the following outcomes for up to five years: factor VIII activity level, frequency of factor VIII use, number of bleeding episodes for up to five years. At the time of this review, patients in cohorts 1, 2 and 3 have been followed for four years, while patients in cohort 4 have been followed for three years.

The two patients enrolled in the lower dosed cohorts (cohort 1 & 2) did not achieve the pre-specified primary endpoint of factor VIII activity levels of 5 IU/dL at week 16 after gene transfer. At three years of follow up, both patients still had low factor VIII levels (< 1 IU/dL).[10,13] These lower doses are not anticipated to be used clinically and, as such, the lower dosed cohorts (cohort 1 and 2) are not described in the Clinical Benefits section of this review. However, safety data were supplemented with evidence from these low-dose cohorts.

Other Trials of Valoctocogene Roxaparvovec

Phase III GENEr8-1

We identified one ongoing open-label, single arm Phase III trial (GENEr8-1).[14,16] GENEr8-1 is evaluating high dose ($6x10^{13}$ vg/kg) valoctocogene roxaparvovec in patients 18 years and older with severe hemophilia A without factor VIII inhibitors who were on prophylactic factor VIII for at least 12 months prior to study entry. Patients with pre-existing immunity to the AAV5 capsid or those who showed any evidence of active infection or immunosuppressive disorder, including HIV infection, were excluded.

The pre-specified primary endpoint of GENEr8-1 was the proportion of patients whose factor VIII levels were ≥ 40 IU/dL. Only limited interim data on 16 patients who had reached 26 weeks as at the April 30, 2019 data-cut have been reported.

Table 4.1. Trials of Valoctocogene Roxaparvovec in Hemophilia A Without Inhibitors

Trials	Study Design	Dose (s) evaluated	Population	Baseline Characteristics	Primary outcomes
NCT02576795 Key trial	Phase I/II open-label dose escalation study	• $6x10^{12}$ vg/kg • 2 $x10^{13}$ vg/kg • $6x10^{13}$ vg/kg • $4x10^{13}$ vg/kg	15 patients aged 18 years or older with severe hemophilia A without inhibitors to FVIII, previously receiving on-demand or prophylactic factor VIII	Median Age: 30 years (range:23-42) Patients with target joint(s): NR N (%) on prophylactic treatment: 14 (93) Mean ABR*: 14 (range: 0-41)	• Number of treatment related AEs • Dose to achieve FVIII activity level of 5 IU/dL at week 16
GENEr8-1	Phase IIII open-label single arm study	• $6x10^{13}$ vg/kg	Patients aged 18 years or older with severe hemophilia A without inhibitors to FVIII, previously on prophylactic factor VIII	Not yet reported	• Change of the median FVIII activity

*Not reported for the one patient who was receiving on-demand treatment at baseline.
ABR: annualized bleed rate, N: number, NR: not reported

Clinical Benefits of Valoctocogene Roxaparvovec

FVIII Activity Level

All seven participants in cohort 3 ($6x10^{13}$ vg/kg dose) and five out of the six participants in cohort 4 ($4x10^{13}$ vg/kg dose) achieved the pre-specified primary endpoint of factor VIII activity levels of 5 IU/dL or more at week 16.[13] At the end of year one, the mean factor VIII activity level in cohort 3 and cohort 4 as measured by chromogenic assay were 64 IU/dl (median: 60 IU/dl; range: 11-88 IU/dl), and 21 IU/dL (median: 23 IU/dl; range: <3-40 IU/dl), respectively. Using categories of hemophilia, all participants in cohort 3, except one who was in the mild hemophilic range, were in the non-hemophilic range at the end of year one. In cohort 4, five participants were in the mild hemophilic range, while one remained in the severe hemophilic range at the end of year one. Of note, the results of the factor VIII activity level using the less conservative one-stage assay showed levels that were approximately 1.6-times as high as those observed with the chromogenic assay (Year 1 cohort 3 [mean, 104 IU/dl; median, 89 IU/dl]; Year 1 cohort 4 [mean, 31 IU/dl; median, 32

IU/dl]). Over the course of the second year, factor VIII levels decreased in all cohort 3 participants and a majority of cohort 4 participants, resulting in a significant decline in the mean Factor VIII expression (chromogenic assay [Cohort 3: ↓44%; cohort 4: ↓29%]; one-stage assay [Cohort 3: ↓43%; cohort 4: ↓26%]).[10,13] The third and fourth year follow up results showed continued decline in factor VIII expression, albeit slower (Table 4.2 and 4.3). [10,13,18,19] For cohort 3 ($6x10^{13}$ vg/kg dose) participants, the year four data on factor VIII activity as measured by the more conservative chromogenic assay showed one participant in the non-hemophilic range, four participants in the mild hemophilic range, one participant in the moderate hemophilic range, and one participant back in the severe hemophilic range.[18] The one-stage assay measurement two participants in the non-hemophilic range and five in the mild hemophilic range at year four.[18]

Table 4.2. Valoctocogene Roxaparvovec: Factor VIII Activity Over 4 Years in Cohort 3 ($6x10^{13}$ vg/kg) of Phase I/II Study

	Mean FVIII as measured by CS assay			Median FVIII as measured by CS assay		
Follow-up year	Mean (IU/dl)	Δ from previous year (IU/dl)	% Δ from previous year	Median (IU/dl)	Δ from previous year (IU/dl)	% Δ from previous year
Year 1	64	--	--	60	--	--
Year 2	36	-28	↓ 44%	26	-34	↓ 57%
Year 3	33	-3	↓ 8%	20	-6	↓ 23%
Year 4†	24	-9	↓ 27%	16	-4	↓ 20%
	Mean FVIII as measured by one-stage assay			Median FVIII as measured by one-stage assay		
Follow-up year	Mean (IU/dl)	Δ from previous year (IU/dl)	% Δ from previous year	Median (IU/dl)	Δ from previous year (IU/dl)	% Δ from previous year
Year 1	104	--	--	89	--	--
Year 2	59	-45	↓ 43%	46	-43	↓ 48%
Year 3	52	-7	↓ 12%	30	-16	↓ 35%
Year 4†	35	-17	↓ 33%	23	-7	↓ 23%

*CS: Chromogenic.

†measurements based on six of the seven participants (evaluable sample for the 7th participant not available

% Δ: percent change

Table 4.3. Valoctocogene Roxaparvovec: Factor VIII Activity Over 3 Years in Cohort 4 ($4x10^{13}$ vg/kg) of Phase I/II Study

	Mean FVIII as measured by CS assay			Median FVIII as measured by CS assay		
Follow-up year	Mean (IU/dl)	Δ from previous year (IU/dl)	% Δ from previous year	Median (IU/dl)	Δ from previous year (IU/dl)	% Δ from previous year
Year 1	21	--	--	23	--	--
Year 2	15	-6	↓ 29%	13	-10	↓ 43%
Year 3	10	-5	↓ 33%	8	-5	↓ 38%
	Mean FVIII as measured by one-stage assay			Median FVIII as measured by one-stage assay		
Follow-up year	Mean (IU/dl)	Δ from previous year (IU/dl)	% Δ from previous year	Median (IU/dl)	Δ from previous year (IU/dl)	% Δ from previous year
Year 1	31	--	--	32	--	--
Year 2	23	-8	↓ 26%	24	-8	↓ 25%
Year 3	15	-8	↓ 35%	12	-12	↓ 50%

Table 4.4. Valoctocogene Roxaparvovec: Hemophilic Range in Phase I/II study

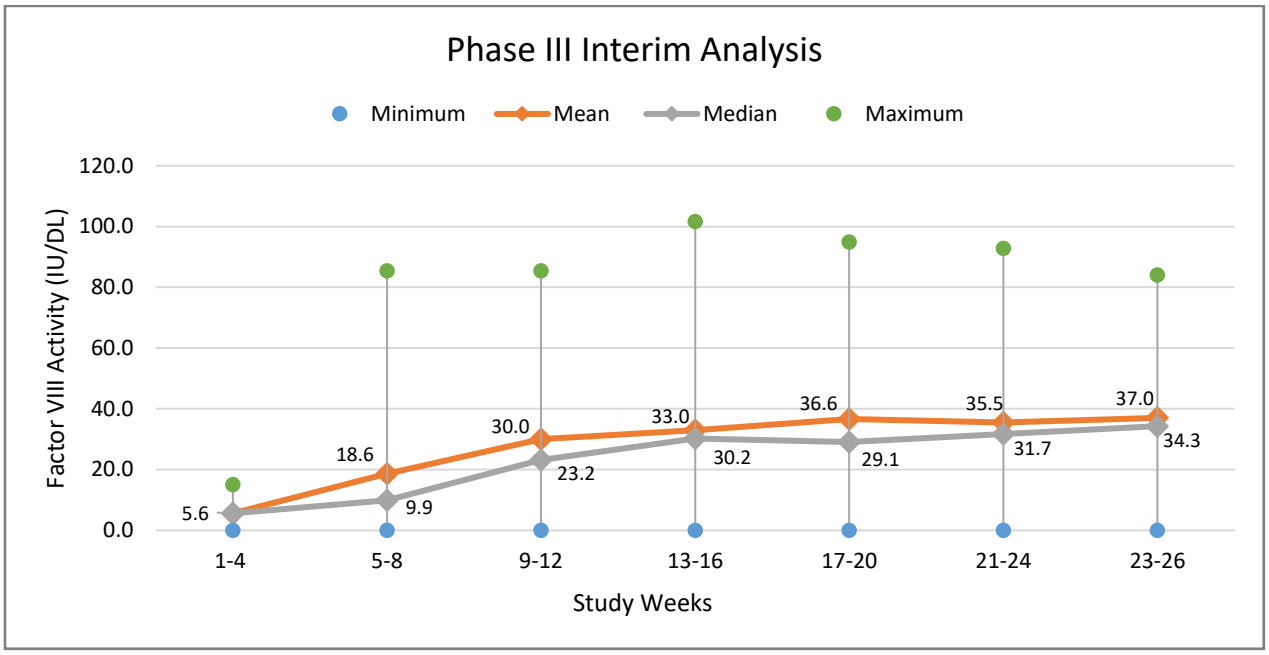
Cohort 3 ($6x10^{13}$ vg/kg); n=7	Hemophilic range as measured by CS over 4 years				Year 4 range as measured by one-stage assay*
	Year 1 (CS)	Year 2 (CS)	Year 3 (CS)	Year 4 (CS)	
Non-hemophilic (>40 IU/dl)	6	2	1	1	2
Mild hemophilia (>5 IU/dl)	0	4	5	4	5
Moderate hemophilia (1-5 IU/dl)	1	1	1	1	0
Severe hemophilia (<1 IU/dl)	0	0	0	1	0
Cohort 4 ($4x10^{13}$ vg/kg); n=6	**Hemophilic range as measured by CS over 3 years**				**Year 3 range as measured by one-stage assay***
	Year 1 (CS)	Year 2 (CS)	Year 3 (CS)		
Non-hemophilic (>40 IU/dl)	0	0	0		0
Mild hemophilia (>5 IU/dl)	5	6	3		5
Moderate hemophilia (1-5 IU/dl)	1	0	2		1
Severe hemophilia (< 1 IU/dl)	0	0	1		0

*Factor VIII activity and hemophilic range (as measured by one-stage assay) for previous years not reported
CS: chromogenic assay
N: number

Of the 16 patients who had reached 26 weeks at the time of the interim analysis in the Phase III trial of $6x10^{13}$ vg/kg valoctocogene roxaparvovec (GENEr8-1), seven had achieved the pre-specified factor VIII levels of 40 IU/dl or greater.[14] Figure 4.1 presents the progression of factor VIII activity as measured by chromogenic assay in the 16 participants from week 1 to week 26. At week 1-4, the mean factor VIII activity level was 5.6 IU/dl (median: 5.6 IU/dl; range:<1-15.1). By week 16, the mean factor VIII activity had risen to 33 IU/dl (median: 30 IU/dl; range: <1-100 IU/dl), after which

the mean factor VIII activity plateaued through week 26 (mean: 36 IU/dl; median: 23 IU/dl; range: <1-84 IU/dl). Measurement by one-stage assay has not been publicly presented.

Figure 4.1. Valoctocogene Roxaparvovec: Factor VIII Activity in Phase III study (Week 1 to Week 26)



Data source: BioMarin Presentation. Bienaime JJ. May 28, 2019. Valoctocogene roxaparvovec Phase II and Phase III update presentation. Figure on slide 18 digitized

Rates of Bleeding Events

Table 4.5 presents data on the mean ABR for 'treated bleeds' for up to four years of follow up in the Phase I/II valoctocogene roxaparvovec trial.[10,13] Data were presented only for the participants who were on factor VIII prophylaxis in the year before the study (6 out of 7 patients in cohort 3 and all 6 patients in cohort 4).

In cohort 3 ($6x10^{13}$ vg/kg dose), the mean ABR for 'treated bleeds' dropped from a baseline of 16.3 events per year (SD:15.7) to a cumulative mean of 0.8 per year, after four years of follow up, representing a 95% reduction.[10,13,18,19] At baseline, only one participant in cohort 3 who had been on factor VIII prophylaxis had zero bleeding events. Following the administration of valoctocogene roxaparvovec, five out of the seven participants in cohort 3 had zero bleeding events in year one of the study; and six out of seven participants had zero bleeding events in year two to year four of the study (Table 4.5). In addition, all participants had full resolution of bleeding in target joints by year two, with continued absence of target joint bleeds in all participants in year 3 (year 4 data not available).

Patients in cohort 4 ($4x10^{13}$ vg/kg dose) also had a large reduction (93%) in the mean ABR for 'treated bleeds' from a baseline of 12.2 (SD:15.4) to a cumulative mean of 0.9 after three years of follow up.[10,13,18,19] In cohort 4, 67% of participants had zero bleeding events at the end of year two and year three, compared to 16% at baseline (Table 4.5). In addition, five of six participants had full resolution of bleeding in target joints by year two, with continued absence of target joint bleeds in the five participants in year three.

In the Phase III trial of $6x10^{13}$ vg/kg valoctocogene roxaparvovec (GENEr8-1), the mean ABR for 'treated bleeds' for the 16 patients who had reached 26 weeks at the time of the interim analysis was 1.5, representing an 86% reduction from a mean of 9.9 events per year. [14]

Table 4.5. Valoctocogene Roxaparvovec: Bleeding Events in the Phase I/II Study

Cohort 3 ($6x10^{13}$ vg/kg; n=7)						
	Baseline	Yr1	Yr2	Yr3	Yr4	Yr1-Yr4
Mean ABR*	16.3	0.9	0.2	0.7	1.3	0.8
Estimated Rate ratio (vs. baseline)	reference	0.06	0.01	0.04	0.08	0.05
No. of Patients Bleed Free (%)	1 (14%)	5 (71%)	6 (86%)	6 (86%)	6 (86%)	---
Cohort 4 ($4x10^{13}$ vg/kg; n=6)						
	Baseline	Yr1	Yr2	Yr3	Yr4	Yr1-Yr3
Mean ABR (SD)	12.2	0.9	1.2	0.5	NA	0.9
Estimated Rate ratio (vs. baseline)	reference	0.07	0.1	0.04	NA	0.07
No. of Patients Bleed Free (%)	1 (17%)	5 (83)	4 (67%)	4 (67%)	NA	---

*The one patient treated with on demand factor VIII at baseline was excluded

Factor VIII Use

Data on mean annualized factor VIII use for up to four years of follow up in the Phase I/II trial of valoctocogene roxaparvovec are presented in Table 4.6. In the year before the study, the mean annualized number of factor VIII infusions per year was 136.7 (SD: 22.4) in cohort 3, and 146.5 (SD: 41.6) in cohort 4.[10,13,18,19] At four years post-administration of valoctocogene roxaparvovec, there was a 96% overall reduction in annualized factor VIII use to a cumulative mean of 5.3 infusions per year.[10,13,18,19] Similarly, the mean annualized rate of factor VIII use in cohort 4 was reduced by 96% to a cumulative mean of 5.7 after three years of follow up.

In the interim phase III results, there was a 95% reduction in the mean annualized factor VIII use after week 5 (to week 26) from 146.1 infusions per year to 6.8 infusions per year.

Table 4.6. Valoctocogene Roxaparvovec: Mean Factor VIII use in the Phase I/II Study

	Baseline	Number of Factor VIII Infusions Per Year			
		Yr1	Yr2	Yr3	Yr4
Cohort 3 ($6x10^{13}$ vg/kg; n=6)	136.7	2.1	8.8	5.5	4.6
Cohort 4 ($4x10^{13}$ vg/kg; n=6)	146.5	2	6.8	8.4	NA

Yr: year
N: number
NA: not applicable

Health-Related Quality of Life (HRQoL)

Haemo-QoL-A, a hemophilia-specific 41-item instrument, scored from 0 (worst) to 100 (best), was used to assess the health-related quality of life in the Phase I/II study. Haemo-QoL-A evaluates 6 health-related quality of life domains: physical functioning, role functioning, worry, bleeding consequences, emotional impact and treatment concerns. In cohort 3, a steady improvement was seen in the Haemo-QoL-A total score of participants over four years of follow-up (Table 4.7).[19] The mean change from baseline observed over the four years of follow-up matched or exceeded the minimum clinically important difference (CID) of 5.5 points.[19]

In cohort 4, participants saw the greatest improvement in Haemo- QoL-A total score at year three (difference of 2.1), however the improvement remained less than the minimum CID of 10 points. Data on the individual Haemo- QoL-A domains were not reported.

No data on health-related quality of life have been reported for the participants in the phase III study.

Table 4.7. Valoctocogene Roxaparvovec: Mean Haemo -QoL-A Total Score in the Phase I/II Study

	Cohort 3 ($6x10^{13}$ vg/kg)			Cohort 4 ($4x10^{13}$ vg/kg)		
	N	Haem-A-QoL total score	Haem-A-QoL Δ from baseline	N	Haem-A-QoL total score	Haem-A-QoL Δ from baseline
Baseline	7	71.8	reference	6	80.9	reference
Year 1	7	81.4	9.6	4	82.4	1.5
Year 2	5	86.2	14.4	6	77.7	-3.2
Year 3	6	87.0	15.2	6	83.0	2.1
Year 4	5	88.0	16.2	NA	NA	NA

Data source: BioMarin Investor Call June 17, 2020. World Federation of Hemophilia Virtual Summit Update. First in Human Four-year Follow-up Study of Durable Therapeutic Efficacy and Safety: AAV Gene Therapy with Valoctocogene Roxaparvovec for Severe Hemophilia A. Figure on slide 11 digitized change.

Also, we evaluated data from the Patient-Reported Outcomes, Burdens, and Experiences (PROBE) project designed to evaluate the health status and the health-related quality of life of hemophilia patients with different phenotypes.[20] The PROBE questionnaire comprises three domains: general

health problems (pain, mobility, and absence from school or work), hemophilia specific problems (e.g., presence of target joints, number of bleeds in the past 12 months), and health-related quality of life (using the EQ-5D-5-L and EQ-VAS tools).[20] Published data on the PROBE study showed that patients in the non-hemophilic range had better general health status and health-related quality of life compared to those in the mild to moderate hemophilia range (mean PROBE score: 0.909 vs. 0.786 [mild] to 0.727 [moderate]; p<0.001).[20] Additional academic-in-confidence data submitted by the PROBE investigators also showed that patients in the mild hemophilic range had a better PROBE score than those in the severe hemophilic range. As described above, most patients treated with valoctocogene roxaparvovec were in the non-hemophilic or mild hemophilic for at least three to four years. These data provide indirect evidence of improved health status and health-related quality of life for valoctocogene roxaparvovec treated patients while in the mild to non-hemophilic range. It is important to note, however, that this is an imperfect inference. Patients received valoctocogene roxaparvovec no earlier than late adolescence, and as may have incurred irreversible effects of hemophilia (e.g., joint damage) prior to treatment. As such, achieving, as an adult, factor VIII levels typical of mild hemophilia is unlikely to achieve quality of life equal to that seen in an adult who has had similar levels throughout his life.

Mortality

We did not identify any studies that assessed the impact of valoctocogene roxaparvovec on mortality.

Other Outcomes

We did not identify any studies that assessed the impact of valoctocogene roxaparvovec on the other outcomes of interest, including chronic pain, mental health status, or health care system utilization. These three outcomes are part of a core set of outcomes developed for assessing gene therapies for hemophilia.[70] We also did not identify outcomes for families and caregivers.

Harms of Valoctocogene Roxaparvovec

All participants in the Phase I/II trial of valoctocogene roxaparvovec experienced one or more adverse events. [10,13] The most common treatment-related AE was elevation of the alanine aminotransferase (ALT) level, occurring in 86% of patients in cohort 3 and 67% of patients in cohort 4. Participants in the lower dosed cohorts (cohort 1 and 2) did not experience elevations in ALT levels. None of the enzyme elevations were accompanied by markers of cholestasis or were associated with symptoms suggestive of liver dysfunction. As noted above, participants in cohort 3 received glucocorticoid prophylactically in response to the enzyme elevation noted in the first patient in the cohort, while participants in cohort 4 were treated with glucocorticoid only if required clinically (due to a protocol amendment). Serious adverse events occurred in three participants over three years of follow up. Two of the three had events considered by the

investigators to be unrelated to treatment (elective total knee replacements surgery for preexisting hemophilic arthropathies). The third patient presented with transient infusion-associated reactions (myalgia, headache, and grade 2 fever) within 24 hours after administration of valoctocogene roxaparvovec; all symptoms resolved within 48 hours after treatment with acetaminophen. Two new serious adverse events considered by the investigators to be unrelated to treatment (details not reported) were reported in the newly released data on year four. [19]

Similar to the Phase I/II trial, the most common treatment-related AE observed in the ongoing Phase III trial as of the data cutoff date was elevation of the ALT level (17 participants, 77%).[14] Other common adverse events observed were nausea (50%), headache (46%), fatigue (41%), and aspartate aminotransferase (AST) elevation (36%). Three participants reported serious adverse events, two of which were judged to be treatment related (details not reported).[14]

There was no new development of factor VIII inhibitors in either trial. All participants developed anti-AAV5 antibodies in the phase I/II study. No data on anti-AAV5 antibody have been reported for the participants in the phase III study.

Table 4.8. Valoctocogene Roxaparvovec: Adverse Events Reported in Phase I/II & Phase III Studies

	Phase I/II			Phase III
	Cohort 1 & 2 (lowest dosed cohorts)	Cohort 3 ($6x10^{13}$ vg/kg)	Cohort 4 ($4x10^{13}$ vg/kg)	$6x10^{13}$ vg/kg
No. of patients	2	7	6	22
Duration of follow-up reported	3 years	3 years	2 years	26 weeks
No. of participants (%)				
AEs	2 (100)	7 (100)	6 (100)	NR
Serious AEs	0 (0)	2 (29)	1 (17)	3 (14)
AEs leading to discontinuation	0 (0)	0 (0)	0 (0)	0 (0)
ALT elevations	0 (0)	6 (86)	4 (67)	17 (77)
Inhibitor development	0 (0)	0 (0)	0 (0)	0 (0)
AAV5 antibody development	2 (100)	7 (100)	6 (100)	NR
Deaths	0 (0)	0 (0)	0 (0)	0 (0)

AE: adverse event
SAE: serious adverse event
ALT: Alanine aminotransferase

Trials of Emicizumab

We identified three trials of emicizumab that met our inclusion criteria (Table 4.9). We did not identify any RCTs directly comparing emicizumab to factor VIII prophylaxis or valoctocogene roxaparvovec gene therapy.

Key Trial of Emicizumab

HAVEN 3

Evidence to inform our assessment of emicizumab in patients with severe hemophilia without inhibitors was mainly derived from HAVEN 3, a Phase III, open-label, multicenter RCT.[21] The trial enrolled 152 male patients aged 12 years and older with severe hemophilia without factor VIII inhibitors who were receiving on-demand or prophylactic factor VIII treatments. Patients who received treatment for thromboembolic disease within the last 12 months or were currently symptomatic with thromboembolic disease were excluded.

Patients receiving on-demand factor VIII treatment before the start of the study (n=89) were randomized in a 2:2:1 ratio to 1.5 mg/kg of emicizumab once weekly (group A) or 3 mg/kg of emicizumab every 2 weeks (group B) or no prophylaxis (group C) for at least 24 weeks. Randomization was stratified by the number of bleeding episodes in the preceding 6 months (< 9/≥ 9 bleeding episodes). The remaining 63 patients who were on routine prophylaxis with factor VIII were assigned to receive 1.5 mg/kg of emicizumab prophylaxis once weekly in a separate cohort (group D), following participation in a 24-week non-interventional (observational) study. All patients on emicizumab prophylaxis initially received four loading doses of 3 mg/kg of emicizumab weekly before transitioning to the assigned dosing schedule. Patients received investigator-determined doses of factor VIII treatment for breakthrough bleeding events.

The median age of patients in HAVEN 3 was 38 years (range: 13-77). Of note, only one patient was less than 18 years of age. Among patients who were previously receiving on-demand factor VIII treatment, about a quarter had experienced fewer than nine bleeding events in the 24 weeks before trial entry, and about 85% had reported one or more target joints at baseline. In contrast, a majority of patients (84%) who had been on factor VIII prophylaxis had experienced fewer than nine bleeding events in 24 weeks before trial entry, and less than half (41%) reported one or more target joints at baseline.

The primary outcome of the study was the ratio of annualized bleeding rate (ABR) for treated bleeds between randomized groups. Secondary outcomes were total bleeding rates (treated and untreated), spontaneous and joint bleeding rates, health-related quality of life, and adverse events (AEs). Intraindividual comparisons of bleeding rates were performed for patients in group D, utilizing data collected during the non-interventional period as the comparator. Further information on the study, including baseline characteristics can be found in Appendix Table D1.

Other Clinical Trials of Emicizumab

HAVEN 4

We also identified two non-randomized trials of emicizumab (HAVEN 4 and HOHOEMI).[23] HAVEN 4 was an open label, multicenter, non-randomized Phase III study conducted in patients aged 12 years or older with severe hemophilia A with or without inhibitors to FVIII, previously on on-demand or prophylactic FVIII.[23] The study consisted of a preliminary run-in period to establish pharmacokinetics in seven patients, and a subsequent expansion phase to assess efficacy and safety in 41 patients. Patients were given 6 mg/kg emicizumab every 4 weeks (preceded by four loading doses of 3 mg/kg weekly) and followed up for at least 24 weeks. At baseline, 98% of patients had severe hemophilia A, 12% had factor VIII inhibitor, 61% had one or more target joint, and 73% were on prophylaxis. The outcomes evaluated included the rate of treated bleeds, health-related quality of life, and AEs.

HOHOEMI

HOHOEMI was also an open label, multicenter, non-randomized study conducted in 13 Japanese children 12 years or younger (weighing > 3 kg) who had severe hemophilia A without factor VIII inhibitors.[24] Patients were administered four loading doses of 3 mg/kg emicizumab every week followed by maintenance doses of 3 mg/kg every 2 weeks (n=6) or 6 mg/kg every 4 weeks (n=7). The median age was 5.4 years (range: 4 months to 10 years), and only one patient had developed a target joint at baseline. All patients but one (a 4-month old baby) had been on factor VIII prophylaxis prior to the study. The outcomes evaluated included the rate of treated bleeds, caregiver's preference, and AEs.

Observational Studies of Emicizumab

McCary 2020 was an observational study conducted in three hemophilia treatment centers in the US.[29] The study enrolled 93 patients with hemophilia who were initiated on emicizumab before May 15, 2019. Data on previous prophylaxis regimen, emicizumab dosing, bleeding events (all bleeds, treated bleeds, joint bleeds, and traumatic bleeds), and thrombotic events were collected retrospectively from 6 months before emicizumab initiation up until October 15, 2019, from chart reviews and patient diaries.

The median age of patients enrolled was 8.6 years (IQR: 4.8-13.5). The majority of included patients did not have inhibitors (n=74). Among the non-inhibitor patients, 66% were 12 years old or younger (n=49), 90% were 18 years or younger (n=66), 86% were on prior factor VIII prophylaxis (n=64), and 16% had one or more target joint (n=12). The outcomes evaluated included annualized bleeding rates (pre- and post-emicizumab initiation), procedural outcomes on patients undergoing invasive procedures, and safety.

Table 4.9. Trials of Emicizumab in Hemophilia A Without Inhibitors

Trials	Study Design	Dose (s) Evaluated	Population	Primary Outcome
HAVEN 3 Key trial	Phase III randomized open label	1.5 mg/kg QW 3 mg/kg Q2W No prophylaxis	152 patients aged 12 years or older with severe hemophilia A *without inhibitors* to FVIII, previously receiving on-demand or prophylactic FVIII	Ratio of treated ABR between randomized groups
HAVEN 4	Phase IIII non-randomized open label	6 mg/kg every 4 weeks (Q4W)	Patients aged 12 years or older with severe hemophilia A *with or without* inhibitors to FVIII, previously receiving on-demand or prophylactic FVIII	Treated ABR in emicizumab arm
HOHOEMI	Phase IIII non-randomized open label	3 mg/kg Q2W 6 mg/kg Q4W	Japanese children less than 12 years (and weighing over 3 kg) with severe hemophilia A *without* FVIII inhibitors.	Treated ABR in emicizumab arms

ABR: annualized bleed rate, FVIII: factor VIII, QW: Once weekly dosing, Q2W: Every 2 weeks, Q4W: Every 4 weeks

Clinical Benefits of Emicizumab

As described above, we did not identify any RCTs directly comparing emicizumab to factor VIII prophylaxis or valoctocogene roxaparvovec gene therapy. However, we identified one RCT (SPINART) that allowed us to indirectly compare emicizumab to factor VIII prophylaxis.[27,28]

The SPINART trial was an open label, multicenter RCT that compared prophylaxis with recombinant factor VIII (Kogenate FS) with no prophylaxis (i.e. on-demand factor VIII treatment). The trial included 84 male patients aged 12-50 years with severe hemophilia without factor VIII inhibitors who were receiving on-demand treatment for greater than 12 consecutive months in the past five years. The trial randomly assigned patients in a 1:1 ratio to routine prophylaxis group (25 IU/Kg 3 times weekly) and to no prophylaxis group for three years. As discussed below, this dose of factor VIII is lower than is typically used today in the US. Randomization was stratified by the presence or absence of a target joint and number of bleeding episodes in the preceding 6 months (< 15/≥ 15 bleeding episodes). Dose adjustment (up to 30 IU/Kg in year 1, and 35 IU/Kg in year 2) in the prophylaxis arm was possible in patients with 12 or more bleeding episodes per year. At baseline, the median age of patients in SPINART was 31 years (range: 15-50), the median number of bleeding episodes in the preceding year was 18 (range: 6-47), and 70% of patients had one or more target joints.

SPINART was found to be sufficiently similar to HAVEN 3 in terms of baseline characteristics, study design, and outcome definitions to allow NMA (see Table 4.10). The major difference noted between the two trials was the study durations (6 months vs. 3 years). However, this was not expected to affect NMAs of bleeding rates, as these outcomes were annualized. As an example,

results from the SPINART trial showed similar annualized bleeding rate ratio on treated bleeds for factor VIII prophylaxis versus no prophylaxis at 1.7 years (rate ratio [RR]: 0.06; 95% CI: NR) and at three years (RR: 0.06; 95% CI: 0.04, 0.1) (See Appendix Tables D7 and D8).

Table 4.10. Key Trial of Emicizumab (HAVEN 3) and FVIII Prophylaxis (SPINART)

Interventions	Inclusion Criteria	Treatment Duration	Key Baseline Characteristics
HAVEN 3 Randomized Arms QW Emicizumab (1.5 mg/kg, n= 36) Q2W Emicizumab (3 mg/kg, n=35) No prophylaxis (n=18)	12 years and older with severe hemophilia, without factor VIII inhibitors ≥5 bleeding events in the previous 6 months	24 weeks	Median Age: 40 years (range:16-77) Patients <18 years: 1 (1%) Patients with target joint(s): 76 (85%) Patients with <9 bleeding events in prior 6 months: 18 (20%)
SPINART FVIII (Kogenate) Prophylaxis (n=42) No prophylaxis (n=42)	12 years and older with severe hemophilia, without factor VIII inhibitors 6-24 bleeding events in the previous 6 months	3 years	Median Age: 31 years (range:15-20) Patients <18 years: 3 (3.6%) Patients with target joint(s): 70% Median number of bleeds in past 12 months: 18 (range: 4-47)

ABR: annualized bleeding rate, FVIII: factor VIII, QW: Once weekly dosing, Q2W: Every 2 weeks

Rates of Bleeding Events with Emicizumab (Adolescents and Adults, Ages 12 and Older)

Emicizumab Compared to Factor VIII Prophylaxis (Using Network Meta-analysis)

In the HAVEN 3 trial, there were fewer treated bleeds among patients randomized to emicizumab weekly (ABR 1.5) or every two weeks (ABR 1.3) compared to the no-prophylaxis group (ABR 38.2) (RR=0.04, 95% CI: 0.02,0.08 and RR=0.03, 95% CI: 0.02,0.07, respectively) (Table 4.11).[21] Approximately 60% of patients randomized to emicizumab had no bleeding during the follow up period; all patients in the no prophylaxis group had bleeding events. Similarly, differences in favor of emicizumab compared to no prophylaxis were observed in the rates of other secondary bleeding related endpoints including all bleeding events, treated spontaneous bleeds, treated joint bleeds, and treated target joint bleeds (see Table 4.11).

In SPINART, there were fewer treated bleeds at three years among patients randomized to recombinant factor VIII (Kogenate FS) prophylaxis group compared to the no-prophylaxis group (ABR 2.5 vs. 37.2; RR=0.06, 95% CI: 0.04, 0.1) (Table 4.11). Similarly, there were fewer treated joint bleeds with factor VIII prophylaxis compared to no prophylaxis (ABR 1.9 vs. 28.7; RR=0.06, 95% CI: 0.04, 0.12). We found no data on all bleeding events, treated spontaneous bleeds, and treated

target joint bleeds. The mean adherence in the prophylaxis arm was 93%, and 88% of patients had at least 80% adherence to factor VIII frequency and prescribed doses. The median prophylaxis dose in the trial was 26.6 IU/kg three times weekly.

Table 4.12 and 4.13 shows the results of the NMAs on the bleeding outcomes – treated bleeds and treated joint bleeds - of emicizumab versus factor VIII prophylaxis. The result of the NMA showed there was a non-significant lower rate of treated bleeds with emicizumab prophylaxis compared to factor VIII prophylaxis (RR=0.57, 95% CI: 0.22, 1.47). Similarly, NMA results showed a non-significant lower rate of treated joint bleeds on emicizumab prophylaxis compared to factor VIII prophylaxis (Table 4.13).

Table 4.11. Bleeding Outcomes Reported in HAVEN 3 and SPINART

Bleeding Outcomes	HAVEN 3			SPINART	
	Emicizumab QW	Emicizumab Q2W	No prophylaxis	Factor VIII Prophylaxis	No prophylaxis
Treated Bleeds					
Mean ABR	1.5 (0.9–2.5)	1.3 (0.8–2.3)	38.2 (22.9–63.8)	2.5 (4.7)	37.2 (19.9)
Rate Ratio	0.04 (0.02–0.08)	0.03 (0.02–0.07)	control	0.06 (0.04 – 0.1)	control
All Bleeds (treated + untreated)					
Mean ABR	2.5 (1.6–3.9)	2.6 (1.6–4.3)	47.6 (28.5–79.6)	NR	NR
Rate Ratio	0.05 (0.03–0.10)	0.06 (0.03–0.10)	Control	--	--
Treated Spontaneous Bleeds					
Mean ABR	1.0 (0.5–1.9)	0.3 (0.1–0.8)	15.6 (7.6–31.9)	NR	NR
Rate Ratio	0.06 (0.03–0.15)	0.02 (0.01–0.06)	Control	--	--
Treated Joint Bleeds					
Mean ABR	1.1 (0.6–1.9)	0.9 (0.4–1.7)	26.5 (14.7–47.8)	1.9 (4.1)	28.7 (18.8)
Rate Ratio	0.04 (0.02–0.09)	0.03 (0.02–0.07)	Control	0.06 (0.04-0.12)	control
Treated Target Joint Bleeds					
Mean ABR	0.6 (0.3–1.4)	0.7 (0.3–1.6)	13.0 (5.2–32.3)	NR	NR
Rate Ratio	0.04 (0.02–0.09)	0.03 (0.02–0.07)	Control	--	--

ABR: annualized bleeding rate, FVIII: factor VIII, QW: Once weekly dosing, Q2W: Every 2 weeks

Table 4.12. NMA Results of Annualized Treated Bleeds: Rate Ratio (95% Credible Interval)

Emicizumab		
0.57 (0.22, 1.47)	FVIII prophylaxis	
0.03 (0.02, 0.07)	0.06 (0.03, 0.11)	On-demand FVIII

Table 4.13. NMA Results of Annualized Treated Joint Bleeds: Rate Ratio (95% Credible Interval)

Emicizumab		
0.53 (0.2, 1.39)	FVIII prophylaxis	
0.03 (0.02, 0.07)	0.07 (0.03, 0.12)	On-demand FVIII

Emicizumab Compared to Factor VIII Prophylaxis (using data from the non-interventional study)

As described above, all patients in HAVEN 3 who had previously received prophylactic treatment with factor VIII were assigned to receive weekly emicizumab prophylaxis in the non-randomized arm.[21] Of the 63 patients who participated in this arm of the trial, 48 had participated in a prior non-interventional study, which was designed to collect data on bleeding events while patients were on factor VIII prophylaxis (median duration of follow up: 30.1 weeks). An intra-individual comparison was conducted among the 48 patients that participated in the non-interventional study by comparing each person's bleeding outcome during the prior non-interventional study while they were on factor VIII prophylaxis to their bleeding outcomes while on emicizumab in HAVEN 3. The analysis showed a 68% reduction in treated bleeds with emicizumab prophylaxis compared to factor VIII prophylaxis (ABR: 1.5 vs. 4.8, RR=0.32, 95% CI: 0.20, 0.51). There appeared to be a similar relative reduction in all bleeds (see Table 4.14). We found no data on the other bleeding outcomes.

Analysis of adherence to factor VIII prophylaxis was conducted in 41 of the 48 patients who participated in the non-interventional study. The analysis showed that only 21 patients (51%) had at least 80% adherence to factor VIII frequency and prescribed doses. The analysis did not report how many patients fully adhered to the prescribed doses. Among the participants who had at least 80% adherence to factor VIII frequency and prescribed dose, the ABR for "treated bleeds" was 4.3 events.

Table 4.14. Emicizumab Prophylaxis versus Prior Factor VIII Prophylaxis in HAVEN 3 Trial

	ABR* (95% CI)		Rate Ratio (95% CI)
	Emicizumab QW (N=48)	Prior Factor VIII	Emicizumab QW vs. Prior Factor VII
Treated bleeds	1.5 (1.0-2.3)	4.8 (3.2-7.1)	0.32 (0.20-0.51)
All bleeds	3.3 (2.2-4.8)	8.9 (5.7-13.9)	0.37† (NR)

ABR: annualized bleeding rate, QW: Once weekly dosing (1.5 mg/kg)
*ABR was calculated by using a negative binomial regression model to determine bleeding rate per day, which was then converted to an annual rate
†estimated (not reported)

Rates of Bleeding Events with Emicizumab (Children <12 Years)

In children less than 12 years old, we identified one open label, multicenter, non-comparative study (HOHOEMI) that assessed the rate of bleeding events in 13 Japanese children while on emicizumab (Table 4.15).[24] The trial evaluated two maintenance doses of emicizumab (3 mg/kg every 2 weeks [Q2W] or 6 mg/kg every 4 weeks [Q4W]) in two cohorts. The ABR for "treated bleeds" in the Q2W and Q4W cohorts were 1.3 (95% CI: 0.6, 2.9) and 0.7 (95% CI: 0.2, 2.6), respectively. In 92% of the patients (n=12), individual ABRs for "treated bleeds" decreased or remained zero while on emicizumab compared to the pre-treatment period. However, details around how the bleeding events in the pre-treatment period was collected was not reported. Other related bleeding outcomes are presented in Table 4.15.

Table 4.15. Emicizumab Bleeding Outcomes Reported in HOHOEMI

Types of Bleed	Mean ABR (95% CI)	
	Q2W (n=6)	Q4W (n=7)
Treated Bleed	1.3 (0.6-2.9)	0.7 (0.2-2.6)
All Bleeds (treated + untreated)	14 (7.6-26)	22 (9.2-52)
Treated Spontaneous Bleeds	0.2 (0.0-1.6)	NE
Treated Joint Bleeds	0.9 (0.3-2.3)	NE
Treated Target Joint Bleeds	NE	NE

CI: confidence interval, NE: not estimable, Q2W: every four weeks, Q4W: every four weeks,

We also identified one observational study (McCary 2020) conducted in patients with a median age of 8.6 years (IQR: 4.8-13.5).[29] Among 39 children without inhibitors in the study, all of whom had been receiving factor VIII prophylaxis, fewer treated bleeds were observed in the six months after initiating emicizumab (ABR: 0.2, 95% CI: 0.0, 0.5) compared to the pre-emicizumab period (ABR: 1.1, 95% CI: 0.5, 2.2). Similarly, there was a significant increase in the percentage of patients with zero bleeding events in the six months after initiating emicizumab compared to the pre-emicizumab period (94% vs. 73%).

Health-Related Quality of Life

Haem-A-QoL, a hemophilia-specific 46-item instrument, was used to assess health-related quality of life in HAVEN 3 and HAVEN 4. Haem-A-QoL evaluates 10 health-related quality of life domains: physical health, feelings, view of oneself, sports and leisure, work and school, treatment, future, family planning, partnership, and sexuality.[54] At week 25, the observed differences between the no prophylaxis arm and the two emicizumab arms (QW and Q2W) in the Haem-A-QoL physical health domain score were 12.5 points and 16.0 points, respectively.[21] Although not statistically significant, the differences exceeded the minimum clinically important difference of 10 points. In the single-arm HAVEN 4 trial, a mean change from baseline of 15.4 (95% CI 7.8, 22.4) was observed in the Haem-A-QoL physical subscale, which exceeded the minimum clinically important difference of 10 points.[23]

In addition, more employed participants in HAVEN 3 (91%) and HAVEN 4 (93%) had no missed days of work at week 25 compared to the 28 days prior to study enrollment (HAVEN 3: 76%; HAVEN 4: 79%).[26] Data on the other Haem-A-QoL domains were not reported in HAVEN 3 and HAVEN 4. We did not identify any data on Haem-A-QoL or any other quality of life measure for the before (factor VIII prophylaxis) and after (emicizumab) comparison in HAVEN 3, or any data that allowed for indirect comparison on this outcome.

Emicizumab Preference Survey

Evaluation of treatment preference (emicizumab vs. factor VIII prophylaxis) was conducted in HAVEN 3 and the two single arm studies (HAVEN 4 and HOHEMI) using emicizumab preference (EmiPref) survey.

In the before and after comparison done in HAVEN 3, 98% of patients favored emicizumab over factor VIII prophylaxis.[21] In HAVEN 4, all participants who were previously on factor VIII prophylaxis preferred emicizumab over their previous factor VIII treatment regimen. [23] Similarly, all caregivers reported a preference for emicizumab over the patient's previous factor VIII prophylaxis in the non-randomized open-label study conducted in Japanese children (HOHEMI).[24] Reasons for preference for emicizumab were not provided in HAVEN 3 and HAVEN 4. However, in HOEHEMI, all caregivers indicated the lower frequency of treatment and easier route of administration as the major reasons for their preference for emicizumab.[24]

Mortality

We did not identify any studies that assessed the impact of prophylaxis with emicizumab or factor VIII prophylaxis on mortality.

Other Outcomes

We did not identify any studies that assessed the impact of prophylaxis with emicizumab on the other outcomes of interest, including chronic pain, mental health status, or health care system utilization that are part of the core data set for gene therapy discussed above.[70] We also did not identify outcomes for family and caregivers, particularly of younger children with hemophilia A.

Harms of Emicizumab

About 85% of patients on emicizumab prophylaxis in HAVEN 3 experienced one or more adverse events.[21] The most common treatment-related AE was injection site reaction, occurring in 25% of patients on emicizumab prophylaxis.[21] Most of the AEs were reported to be mild. There was a total of 14 serious AEs in patients on emicizumab prophylaxis in HAVEN 3 (4 bleeding events, 1 cardiac disorder, 3 cases of infection, 3 musculoskeletal disorders, 1 psychiatric disorder, 1 trauma case, and 1 loosening of orthopedic device), none of which were considered by the investigators to be treatment-related. Similar patterns of AEs were observed in the two other emicizumab trials, with very few serious AEs and those that occurred were also deemed not to be related to emicizumab (Table 4.16). There were no reports of thrombotic microangiopathy, thromboembolism, hypersensitivity reactions, new development of factor VIII inhibitors, serious AEs related to co-exposure to emicizumab and factor VIII prophylaxis, or deaths in any of the trials.

Table 4.16. Emicizumab Adverse Events Reported in HAVEN 3, HAVEN 4 & HOHEMI

	HAVEN 3 (randomized and non-randomized arm, adults*)	HAVEN 4 (non-randomized, adults)	HOHEMI (non-randomized, children)
No. of patients	150	41	13
Median duration of exposure	29 weeks	25.6 weeks	
No. of participants (%)			
AEs leading to discontinuation	1 (1)	0 (0)	0 (0)
Injection site reaction	38 (25)	9 (22)	1 (8)
Thrombotic/Thromboembolic	0 (0)	0 (0)	0 (0)
Thrombotic Microangiopathy	0 (0)	0 (0)	0 (0)
Inhibitor development	0 (0)	0 (0)	0 (0)
Deaths	0 (0)	0 (0)	0 (0)

AE: adverse events

Uncertainty and Controversies

The evidence on valoctocogene roxaparvovec has multiple limitations creating uncertainties:

- Very few patients have been studied, particularly at the likely dose of $6x10^{13}$ vg/kg
- Duration of follow-up is currently limited and factor VIII levels are declining over time leading to uncertainties in the duration of benefit
- Interim data from the phase III trial suggest lower rates of success in achieving factor VIII levels ≥ 40 IU/dL than in the phase I/II trial, however complete interim data have not been released
- The studies have been single arm with no control group

The manufacturer of valoctocogene roxaparvovec has suggested that the low bleeding rates 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 since mild and moderate hemophilia are typically the result of a mutation that may alter the functional capacity of factor VIII as well as its expression. This appears to be a *post hoc* explanation for results based on a small number of data points. Additionally, annualized bleeding rates are felt to be an insufficient measure of benefit in patients receiving prophylaxis for hemophilia as patients with low factor levels are believed to experience "micro-bleeds" that lead to pain and ongoing joint damage.

Valoctocogene roxaparvovec targets hepatocytes rather than endothelial cells, the liver cells that normally produce factor VIII. It is uncertain whether over the long term this could result in chronic liver inflammation or other liver disorders, or if expression could wane in patients with chronic HCV infection whose fibrosis progresses.[30] Concerns have also been expressed in the hemophilia community that low level inflammation related to transfection with AAV5 could lead to long-term liver damage as has been seen with chronic hepatitis C infection and that these harms might take many years to become apparent.

Patients who are treated with valoctocogene roxaparvovec typically develop antibodies to AAV5. This may prevent retreatment with valoctocogene roxaparvovec or treatment with another therapy using AAV5, but it is also possible that in the future it will be possible to overcome antibody development or that other gene therapy vectors will be preferred.

As discussed in ICER's prior report, the development of inhibitors has very important implications for management, costs, and quality of life. Emicizumab is being used for prophylaxis including in patients with little to no prior exposure to FVIII. There is no high-quality evidence assessing how emicizumab used in this way affects the rate of inhibitor development. Use of emicizumab in very young children will likely affect the natural history of the development of inhibitors to factor VIII.

We heard expert opinion that it could increase or decrease the risk of developing inhibitors. Since emicizumab precludes the need for prophylaxis with factor VIII, factor VIII exposures will be infrequent with a protracted timeline of accumulating total exposure to factor VIII occurring over years rather than months, potentially reducing the overall incidence of inhibitors. However, it may also increase the risk of inhibitor formation since early exposures to FVIII will occur in the context of acute treatment events (e.g., trauma or surgery) which may involve increased intensity of FVIII exposure. A randomized clinical trial is comparing emicizumab to factor VIII (Eloctate) in the prevention of inhibitors (see Appendix C).[31]

The RCT evidence on factor VIII that was most comparable to HAVEN 3 comes from a trial that used substantially lower doses of factor VIII than are typically used in the US today. We do not have a randomized trial using these higher doses of factor VIII prophylaxis. As such, the best RCT evidence comparing emicizumab with factor VIII prophylaxis is indirect both because the therapies were studied in different trials and because the dose of factor VIII studied was lower than the appropriate comparator dose. Additionally, within an NMA comparing these therapies, there are wide confidence intervals around the point estimates of effect.

We chose to compare emicizumab with factor VIII prophylaxis using results of each from randomized trials. If reductions in adherence outside of trials are not similar for the two therapies this 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.

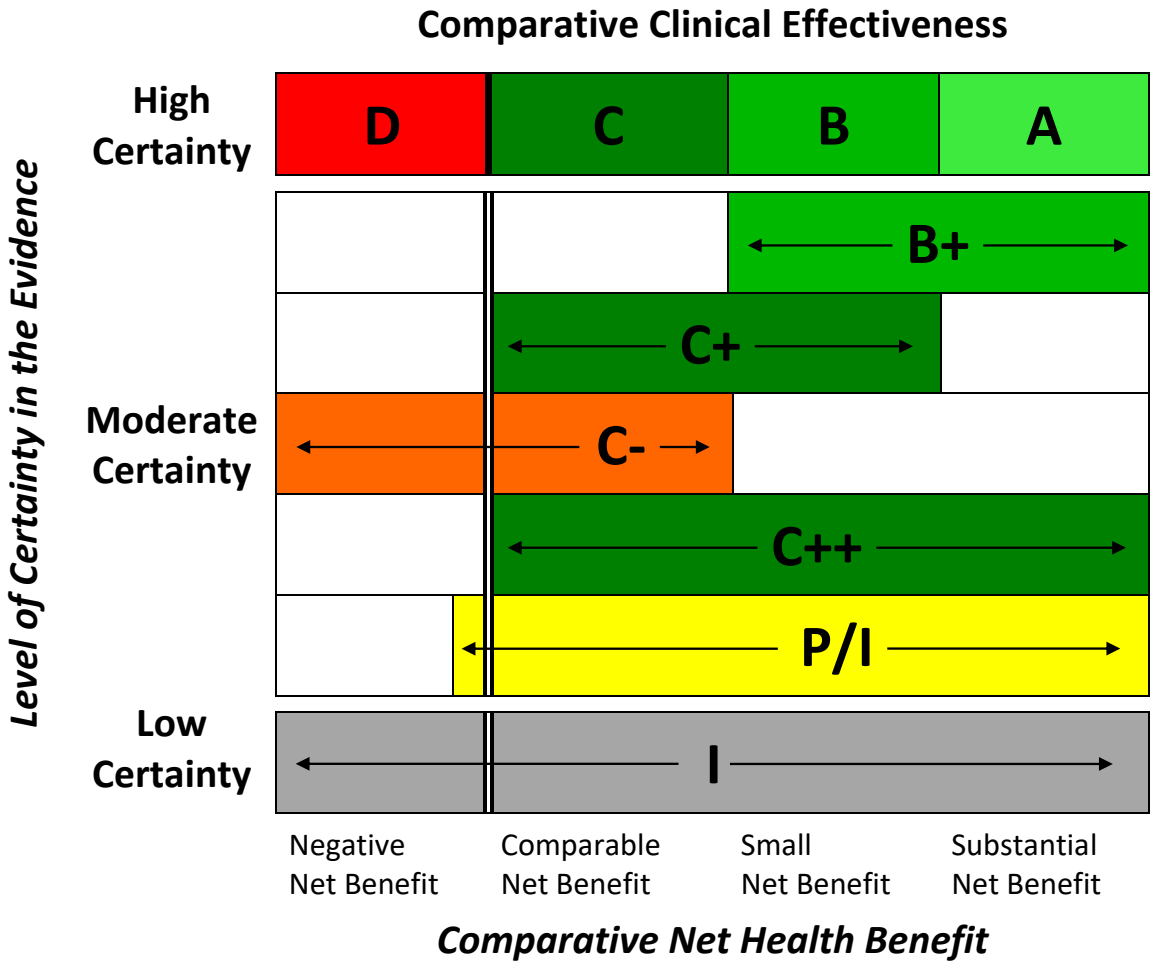
Emicizumab remains a relatively new treatment and unanticipated harms could still be found. We have greater reassurance compared with our prior evaluation of emicizumab as it has now been used much more widely and for longer periods, and so clinical experience has reduced (but not eliminated) these concerns.

Heterogeneity and Subgroups

We are uncertain whether the relative benefits of emicizumab versus factor VIII prophylaxis in children and adults are the same. We were not able to explore this further because of insufficient data. The only identified study of emicizumab that was conducted in children aged 12 years or younger without inhibitors to factor VIII (HOHOEMI) did not have a control arm.

4.4 Summary and Comment

Figure 4.2. ICER Evidence Rating Matrix



A = "Superior" - *High certainty of a substantial (moderate-large) net health benefit*
B = "Incremental" - *High certainty of a small net health benefit*
C = "Comparable"- *High certainty of a comparable net health benefit*
D= "Negative"- *High certainty of an inferior net health benefit*
B+= "Incremental or Better" – *Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+ = "Comparable or Incremental" - *Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit*
C- = "Comparable or Inferior" *– Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit*
C++ = "Comparable or Better" - *Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I = "Promising but Inconclusive" *- Moderate certainty of a small or substantial net health benefit, small likelihood of a negative net health benefit*
I = "Insufficient" – *Any situation in which the level of certainty in the evidence is low*

Table 4.17. ICER Evidence Ratings

Interventions	ICER Evidence Rating
Valoctocogene Roxaparvovec vs. Factor VIII Prophylaxis	P/I
Emicizumab vs. Factor VIII Prophylaxis	C++
Valoctocogene Roxaparvovec vs. Emicizumab	I

Valoctocogene Roxaparvovec Compared with Factor VIII Prophylaxis

Current evidence for valoctocogene roxaparvovec has important limitations. We are uncertain about the initial success rate, the initial levels of factor VIII achieved, and the duration of benefit. That said, it is clear that many patients who are successfully treated have their hemophilia signs and symptoms eliminated or reduced to a mild state, at least for a period of years.

Successfully treated patients require no frequent therapies, and so it is far less burdensome than factor VIII prophylaxis. Additionally, adherence to an ongoing therapy is no longer required, although monitoring of factor levels over time remains important.

Liver inflammation can occur acutely with valoctocogene roxaparvovec, but this has typically not been a severe problem. More concerning is the possibility that antibodies to AAV5 could interfere with other treatments including other, perhaps more durable, gene therapies for hemophilia A and treatments or vaccines for conditions such as cancer or infectious diseases.[32,33] An additional concern is whether therapy with valoctocogene roxaparvovec could lead to chronic liver inflammation, perhaps because the transfected cells are not the cells that normally produce factor VIII.

Overall, there are clear clinical benefits for many patients treated with valoctocogene roxaparvovec, but the durability of these benefits, the implications for disqualification from treatment with other AAV5 therapies, and potential long-term harms such as liver disease are all uncertain. We have moderate certainty of a small or substantial benefit of valoctocogene roxaparvovec compared with factor VIII prophylaxis, but a nonzero likelihood of net harm. As such, in adults with severe hemophilia A without inhibitors, we rate valoctocogene roxaparvovec compared with factor VIII prophylaxis as "promising but inconclusive" *(P/I)*.

Emicizumab Compared with Factor VIII Prophylaxis

Prophylaxis with either emicizumab or factor VIII is far superior to no prophylaxis in patients with severe hemophilia A. Emicizumab appears to have lower bleeding rates (of all types) compared with the doses of factor VIII used in the SPINART randomized trial, perhaps because it avoids the peak and trough levels that occur with factor VIII prophylaxis. We have less certainty in how the

efficacy of emicizumab compares with the doses of factor VIII now typically used for prophylaxis in the US. These higher doses have additional efficacy, but the magnitude of that additional efficacy is uncertain.

The long-term comparative effects of emicizumab on joint disease are unknown, both in patients who initiate emicizumab as young children and in adults who initiate it and already have established joint disease.

Emicizumab is substantially less burdensome than factor VIII. This is a benefit in itself, but it additionally likely leads to improved adherence and also to more patients choosing prophylaxis rather than on-demand therapy.

Although thrombotic events were an issue with emicizumab when patients with inhibitors received large amounts of a bypassing agent for acute bleeding, this has not been noted in patients without inhibitors who are treated with factor VIII for acute bleeding.

We have high certainty that there is at least a comparable benefit of emicizumab compared with factor VIII prophylaxis at the doses now typically used in the US, and moderate certainty of a small or substantial net health benefit. As such, in patients with severe hemophilia A without inhibitors, we rate emicizumab compared with factor VIII prophylaxis as "comparable or better" *(C++).*

Valoctocogene Roxaparvovec Compared with Emicizumab

Given the lack of head-to-head evidence comparing valoctocogene roxaparvovec with emicizumab and the uncertainties about valoctocogene roxaparvovec described above, in adults with hemophilia A without inhibitors, we rate the evidence comparing valoctocogene roxaparvovec with emicizumab as "insufficient" *("I")*.

5. Long-Term Cost Effectiveness

5.1 Overview

Here we describe the economic evaluation of valoctocogene roxaparvovec and emicizumab as prophylactic therapy for patients with hemophilia A without inhibitors to factor VIII. Refer to the sections above for details on the systematic review of the clinical evidence on this topic.

Our approach is based on accomplishing two primary objectives using Markov models. The first was to estimate the cost effectiveness of valoctocogene roxaparvovec compared to prophylaxis with factor VIII preparations in adult patients with severe hemophilia A without inhibitors to factor VIII. The analysis for this first primary aim followed the ICER ultra-rare disease framework and includes a health care sector perspective (i.e., focus on direct medical care costs only) as a base case using a lifetime time horizon. A societal perspective is presented as a co-base case if the incremental impact of treatment on productivity and other societal costs is substantial and is large in relation to health care costs. Note that even though patients with hemophilia may experience substantial productivity loss, treatments may have similar impacts on productivity, leading to small incremental differences in societal costs between treatments. This was the case here and so the results inclusive of broader societal costs are presented as a scenario analysis. As valoctocogene roxaparvovec is a one-time gene therapy for hemophilia A, this analysis was also conducted using ICER's High-Impact Single and Short-Term Therapies (SST) framework.

The second primary objective was to assess the cost effectiveness of emicizumab relative to prophylaxis with factor VIII preparations for new patients with hemophilia A without inhibitors to factor VIII who are eligible for prophylactic treatment. The base case for the second analysis, follows ICER's standard framework, with a health care sector perspective and a lifetime time horizon, with productivity and other indirect costs considered in a scenario analysis.

5.2 Methods

We developed two *de novo* decision analytic models for patients with hemophilia A without inhibitors to factor VIII (hereafter referred to as without inhibitors), informed by key clinical trials, prior relevant economic models, and other published studies regarding hemophilia A. The first model was used to conduct the evaluation of valoctocogene roxaparvovec in adult patients with severe hemophilia A without inhibitors. The second model was used to evaluate emicizumab in patients with hemophilia A without inhibitors eligible for factor VIII prophylaxis. In each case, the base case took a health care sector perspective with costs and outcomes discounted at 3% per year.

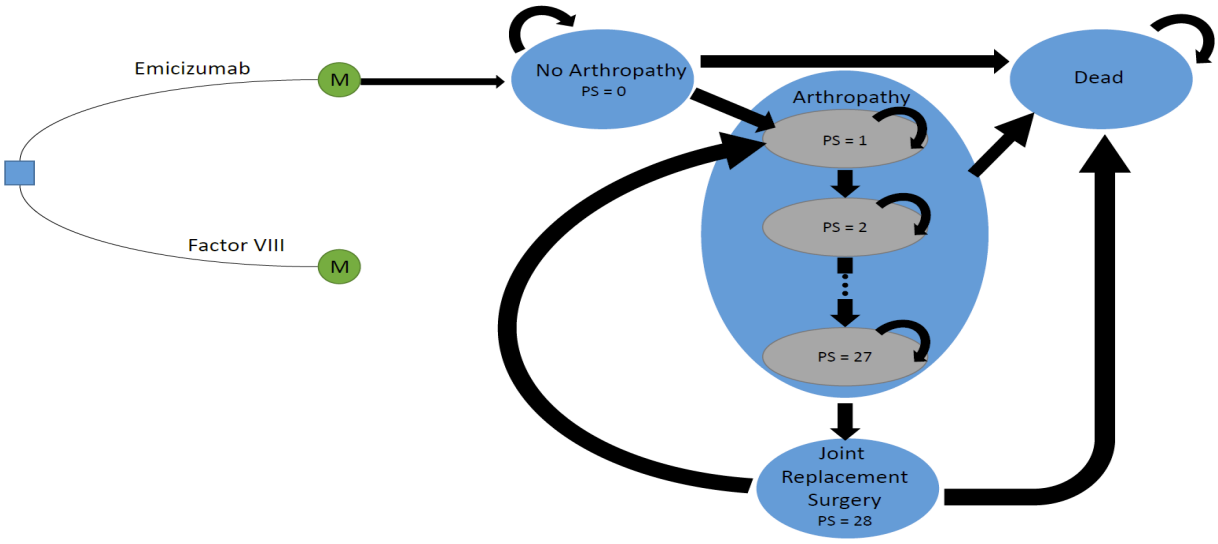
The first model centered on an intention-to-treat analysis, with a hypothetical cohort of adult patients with severe hemophilia A without inhibitors being treated with valoctocogene

roxaparvovec, or factor VIII prophylaxis. The second model focused on an intention-to-treat analysis, with a hypothetical cohort of patients with hemophilia A without inhibitors eligible for prophylaxis for factor VIII being treated with emicizumab or factor VIII. The cycle length in both models was 6 months, based on the literature related to bleed rates and subsequent long-term development of joint damage from target joint bleeds as tracked by Pettersson scores (PS). The models each used a lifetime time horizon for the base case. The models were developed in Excel 2016.

Model Structure

Given the importance of acute bleeds, as well as the long-term joint damage caused by joint bleeds that lead to arthropathy and the potential need for joint replacement surgery, the models were structured using tunnel states corresponding to PS scores that range from 0-28. Upon reaching a PS of 28, the base case model assumed patients have joint replacement surgery and return to a PS of 1. Transitions through the PS states in the models were based on the expected frequency of joint bleeds associated with the treatments and subsequent expected increases in the PS.[34] Patients also had age-varying mortality rates that are not related to PS. Patients with a PS of 0 will be viewed as having "no joints with arthropathy," patients with a PS of 1-27 will be viewed as having "at least one joint with arthropathy," and patients with a PS of 28 will be viewed as "requiring surgery." Hence, while incorporating the tunnel states based on progression through PS, the model may be viewed as having four general health states: no arthropathy, arthropathy, joint replacement surgery, and death. That said, in the first model patients enter as adults and are modeled as starting with the average PS score seen in patients 18 years of age and consequently none of those patients are ever in the "no joints with arthropathy" health state. In the second model, patients begin with a PS score of 0 consistent with being 1 year of age. Figure 5.1 below illustrates the structure of model 2; note that model 1 has a very similar structure but patients start with a PS score of 14. In each cycle, the expected number of bleeds across treatments were modeled along with related costs and impacts on patient utilities. Patients remained in each model until they died. All patients in both models could transition to death from all causes from any of the alive health states.

Figure 5.1. Markov Model Schematic for Model 2



M: Markov node, PS: Pettersson score

Costs and utilities were assigned in each cycle based on numbers of different types of bleeds as well as on patient ages and level of arthropathy in the particular health states.

Target Population

The population of focus for the economic evaluation of valoctocogene roxaparvovec (model 1) is adult males (age 18 and over) with severe hemophilia A without inhibitors who require prophylaxis. The population of focus for the economic evaluation of emicizumab (model 2) is male patients with hemophilia A without inhibitors who require prophylaxis (assumed to start at age 1).

In the base-case analysis for valoctocogene roxaparvovec (model 1), patients enter the model at the age of 18 and start in the average PS for that age reported in the literature, which was 14.[34] In the base-case analysis for emicizumab (model 2), patients enter at age 1 year with a PS of 0.

Treatment Strategies

The list of interventions for these analyses was developed with input from patient organizations, clinicians, manufacturers, and payers on which drugs to include. The full list of interventions is as follows:

- valoctocogene roxaparvovec (Roctavian™, BioMarin Pharmaceutical)
- emicizumab-kxwh (Hemlibra®, Genentech)

Comparators

Each analysis will include the comparator of factor VIII prophylaxis itself modeled using a mix of half-life and extended half-life regimens each with a representative drug for costing. The comparative effectiveness review above rated the evidence for comparing emicizumab to valoctocogene roxaparvovec as insufficient ("I") and so we did not perform a direct economic analysis comparing these two prophylactic strategies.

Key Model Characteristics and Assumptions

Below is a list of key model choices:

- Bleed rates determine transition rates across PS, costs, and utilities in the model.
- Bleed rates for valoctocogene roxaparvovec in the first model were derived from available data on factor levels seen in patients on that treatment and literature-based estimates of bleed rates across factor levels.[35] At projected factor levels below 5%, 5% of patients are assumed to switch to emicizumab prophylaxis. At projected factor levels below 1%, all patients were assumed to switch to emicizumab.
- Bleed rates are taken from the HAVEN 3 trial for emicizumab.
- Bleed rates from a recent published study by Malec et al. examining bleed rates in US hemophilia treatment centers affiliated with the American Thrombosis & Hemostasis Network (ATHN) for patients taking factor VIII prophylaxis were used for the factor VIII arms in each model. Given the way bleeds were captured, we view those rates as an evidence-based lower bound for bleeds associated with current dosing.
- Proportions of all bleeds relative to treated bleeds in the HAVEN 3 trial along with proportions of all bleeds that are joint bleeds in the HAVEN 3 and POTTER trials were used to estimate different types of bleeds relative to treated bleeds for factor VIII and valoctocogene roxaparvovec.
- Factor VIII dosing and costs are based on two representative treatments, Advate for standard half-life, and Eloctate for extended half-life, using doses of those drugs consistent with patients treated with those treatments in US hemophilia treatment centers affiliated with ATHN.

- The model structure was based around the PS. This allows for longer-term cycles while still accounting for bleeds each year as well as the development of arthropathy and the possibility of requiring surgery.
- The model used 6-month cycles. This was the longest standard cycle that allowed for reasonable transition rates between PS counts each cycle, given the expected bleeding rates possible in the model.

- Survival was weighted by health state utilities derived from the published literature.[40,41,43,71,72] The model includes separate utilities for different types of bleed events, varying baseline utility by age and arthropathy, and utility associated with requiring surgery.
- The model included all direct treatment costs associated with each individual regimen, including drug acquisition costs and non-pharmacy costs (including all medical expenses associated with bleeds).
- All costs prior to 2019 were adjusted for inflation following methods outlined in the ICER reference case so that all cost inputs and outputs in the model reflect 2019 US dollars.[73,74]

Our model also included several key assumptions, stated in Table 5.1 below.

Table 5.1. Key Model Assumptions

Assumption	Rationale
Total bleeds relative to treated bleeds are modeled based on the emicizumab arm of the HAVEN 3 trial.[21] Joint bleeds were assumed to be the same percentage of all bleeds for each comparator in base case analyses using a simple average of rates of total joint bleeds to all bleeds seen in the various arms of the HAVEN 3 trial (provided by Genentech) and the proportion seen in the POTTER trial (resulting in 0.66 as the proportion used).[36] [21]	Treated bleeds are most commonly measured, but total joint bleeds have been shown to impact the PS.[36,37] The POTTER trial offered the only published account of all bleeds and all joint bleeds associated with hemophilia A but data were made available from HAVEN 3 as well. There is no clinical reason to believe that the proportion of bleeds that are joint bleeds, or what proportion of all bleeds would be treated, would vary by treatment, and provided data do not suggest any such difference.
Annual bleed rates are equivalent regardless of the degree of arthropathy.	Data on the relative occurrence of bleed events pre- and post-arthropathy are limited. Increasing bleed rates due to arthropathy are explored in a scenario analysis.
Pettersson scores (representing joint arthropathy development) increase as a function of joint bleeds (treated and/or untreated) over time at different rates for patients over and under the age of 25.	Pettersson scores have most recently been reported to increase by one point for every 36.52 joint bleeds (treated and/or untreated) in patients under 25 and by one for every 6.52 joint bleeds for patients over 25.[37]
All patients were assumed to be male, and patient weight and background mortality was based on US male population averages.	Hemophilia is an X-linked recessive disease primarily affecting males. Females with hemophilia A typically have less severe disease. We assume that prophylaxis of hemophilia will not substantially impact weight or mortality.
The utilities associated with a bleed are applied for two days. After two days we assume the bleed state utility is an average of the no bleed and bleed values for the remainder of a week to reflect that the impact of the bleed on utility lingers after the bleeding stops.	The duration of a bleed is estimated to be two days. However, the impact of a bleed likely lingers beyond bleed duration and treatment time. The number of days per week for bleed utilities is varied in a scenario analysis.
Bleed disutilities were derived from patients with inhibitors as opposed to patients without inhibitors and hence the bleed disutility was assumed to be the same for those without inhibitors as seen in those with inhibitors.	The bleed disutilities in the population with inhibitors could potentially be greater than those without inhibitors. Thus, the treatment effect of emicizumab and valoctocogene roxaparvovec may be slightly overestimated. Sensitivity analyses around these bleed utilities were assessed
Cost per treated bleed event is the same for all comparators.	We have not seen evidence to support different on-demand treatment costs for patients on different forms of prophylaxis.

Model Inputs

Clinical Inputs

Bleed Rates

The rates of bleeds seen in Group B of the Haven 3 trial were used for emicizumab. For factor VIII in the base case model, as we opted to use doses consistent with current clinical practice and specifically from provided ATHN data (see below), we also opted to use bleed rates for factor VIII from a recent published study that included self-reported bleed rates from patients with severe hemophilia A or B being treated in US Hemophilia Treatment Centers affiliated with ATHN by Malec et al.[38] Malbec et al. provides an overall rate of bleeds per year (1.3), which we take to be treated bleeds, associated with factor VIII prophylaxis. We view this rate to be an evidence based lower bound of bleed rates associated with factor VIII at currently representative doses. The ratio of treated joint bleeds to treated bleeds and the ratio of treated target joint bleeds to treated joint bleeds seen in Group B of the HAVEN 3 trial for emicizumab was used to estimate treated target joint bleeds from the number of treated joint bleeds for factor VIII. In addition, the ratio of all bleeds to treated bleeds seen in Group B of the HAVEN 3 trial was used to estimate total bleeds for factor VIII. An average of the ratios of all bleeds that were joint bleeds in all the arms of the HAVEN 3 as well as that seen in the POTTER trial were used to estimate total joint bleeds from treated bleeds for emicizumab and factor VIII.[21,36]

Treated bleed rates for valoctocogene roxaparvovec were modeled based on available evidence of treated joint bleed rates across factor levels seen in moderate and mild hemophilia patients by den Uijl et al.[35] To estimate treated joint bleed rates, median one-stage factor VIII levels of high dose patients from BioMarin were combined with estimated rates of treated joint bleeds by factor level in den Uijl et al. In addition, to balance these estimates with lower than usual bleed rates seen in the trials, patients with factor levels above 50 were assumed to have zero bleeds, and patients with factor levels between 1 and 3 percent were assigned the bleed level of those with 3%. Further, we averaged across the tail of the bleed rates for factor levels of 11 and up and assigned that to all those between 50 and 11 and made a slight adjustment (i.e. changed from 0.78 to 0.80) to a non-monotonic portion of the relationship between factor levels and bleeds at factor levels less than 11 after digitizing figure 2 from den Uijl et al.[35] Declines across time in average patient factor levels available at 26 weeks for all patients were projected forward based on proportional declines seen in available data covering years 1-4. The projections also used the average percent declines seen between years 2 and 3 and years 3 and 4 to project year 5 and beyond. Once patients were projected to be at factor levels below 5% (cycle 16), 5% of the patients were assumed to switch treatment, and then once the patients were projected to be at less than 1% (cycle 25), all patients were assumed to switch treatment. Finally, for the first cycle of treatment for valoctocogene roxaparvovec, we assumed patients would experience 3 months with a bleed rate equal to that of factor VIII prophylaxis, and 3 months with a bleed rate of zero.

Estimates of the other types of bleeds for valoctocogene roxaparvovec were then based on the same relative proportions of bleeds used for factor VIII described above. For example, we used the ratio of total treated bleeds to total treated joint bleeds as well as the ratio of total bleeds to total treated bleeds from HAVEN 3 and assumed as described above for the other treatments that 0.66 of all bleeds would be joint bleeds.

Table 5.2 shows the bleed rates used in the model. Selected years are shown for valoctocogene roxaparvovec to give a sense of the variance across time. Across time, based on available data, the factor levels for patients who had received valoctocogene roxaparvovec were projected to decline until patients reached a factor level of 5% at which point 5% of patients were assumed to switch to emicizumab, and then upon reaching a projected factor level less than 1% all patients were modeled as if they are being treated with emicizumab. Bleed rates for valoctocogene roxaparvovec were projected by factor level as described above which can also be seen in Table 5.10 below.

Table 5.2. Annual Bleed Rates

Drug	All Bleeds*	All Joint Bleeds*	Treated Non-Target Joint Bleeds	Treated Target Joint Bleeds
Factor VIII	2.60	1.72	0.60	0.70
Emicizumab	2.60	1.72	0.60	0.70
Valoctocogene Roxaparvovec Year 2	0.45	0.30	0.10	0.12
Valoctocogene Roxaparvovec Year 10	7.05	4.65	1.63	1.90
Valoctocogene Roxaparvovec Year 13	2.60	1.72	0.60	0.70

*Includes treated and untreated bleeds

Infusions

The model will include a projected count of infusions as these may be of interest. Specifically, all treated bleeds will be assumed to incur one infusion. Further, prophylactic treatment with Advate will be counted as 3 infusions per week, and Eloctate will be counted as 1.8 infusions per week.

Transition Probabilities

Transition probabilities between the PS-based health states were 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 one for patients under age 25 and 6.52 joint bleeds result in a one-point PS increase in patients aged 25 years or more.[37] Hence, the annual number of joint bleeds divided by 36.52 and subsequently by 6.52 as patients reach 25 years old can be thought of as an annual transition rate to the next higher PS. Consequently, half the annual bleed rate divided by 36.52 and then 6.52 corresponds to the transition rate using 6-month time cycles. Bleeding rates in the HAVEN 3 trial were only reported for those at or above the age of 12. For the child model, bleed

rates from HAVEN 3 are proportionally lowered based on the observed bleed rates for those aged 12 and older versus those under age 12 in the HAVEN 1 trial. When the child reaches 12 years old, bleed rates from the HAVEN 3 trial are used. Following surgery, all patients (minus those expected to die of all causes) are assumed to return to the arthropathy health state with a PS of 1.

The transition rates corresponding to the bleed rates of the drugs are shown in Table 5.3 and are based on numbers described above related to bleed rates and PS by age in the POTTER trial. The rates will change across time for valoctocogene roxaparvovec based on the projections of factor levels described above. Projections for the first two years are shown below.

Table 5.3. Transition Probabilities Across Pettersson Scores Based on Bleed Rates

Drug	Age < 12	12 ≤ Age < 25	Age ≥ 25
Factor VIII	0.006	0.016	0.085
Emicizumab	0.006	0.016	0.085
Valoctocogene Roxaparvovec Year 1	N/A	0.010	0.056
Valoctocogene Roxaparvovec Year 2	N/A	0.008	0.042

N/A: not available

Discontinuation

The models do not include discontinuation due to lack of available data on discontinuation rates, and it is presumed that patients discontinuing one treatment would most likely switch to one of the other treatments.

Mortality

Age-specific all-cause mortality was sourced from the CDC life tables for males which are representative of the male population in the US.[75] Prophylaxis for hemophilia A in patients without inhibitors has not been demonstrated to decrease mortality,[76] and the mortality rates seen over recent decades may not apply now that there are effective therapies for HIV and hepatitis C and new cases related to factor VIII contamination are unlikely to occur. As such, there is little evidence to suggest a differential mortality effect across options for prophylaxis.

Serious Adverse Events

Serious adverse event data reported in the HAVEN trials for emicizumab, particularly in HAVEN 3, were not significantly associated with the drug. Serious adverse events (SAEs) in data available for factor VIII inhibitors were few and mainly bleed-related. For valoctocogene roxaparvovec, only minor liver inflammation has been reported, which was not deemed to rise to the level of an SAE. Consequently, the models here do not include SAEs.

Heterogeneity and Subgroups

There are insufficient data to derive potential subgroups that may have differential response to therapy.

Utilities

Health state utilities were derived from published literature sources and were applied to the relevant health states. Baseline utility was taken from results of EQ-5D utilities based on responses from hemophilia patients broken out by age and degree of arthropathy, found in Ohara et al. (Table 5.4)[39] All of the disutilities associated with bleeds and with surgery used in the model were measured in patients with hemophilia A using the EQ-5D.[39-43] We used the same health state utility values across treatments evaluated in the model. Utility in the surgery state was modelled using one month of having a time-tradeoff utility found in a general hip replacement pre-surgery patient group reported in the literature in 1993 (0.32), and 5 months with utility corresponding to a PS of 1-27 and the age of the patient getting surgery in the model.[41,42]

Table 5.4. Health State Utilities

Age	Pettersson 0	Pettersson 1-27	Surgery	Source
0-30	0.94	0.82	0.72	O'Hara 2018; Laupacis 1993
31-40	0.84	0.74	0.65	O'Hara 2018; Laupacis 1993
41-50	0.86	0.69	0.61	O'Hara 2018; Laupacis 1993
51-60	0.83	0.63	0.56	O'Hara 2018; Laupacis 1993
61-100	0.73	0.54	0.48	O'Hara 2018; Laupacis 1993

The utility of surgery is based on one month of a utility of 0.32, and 5 months at a utility corresponding to a Pettersson score of 1-27.

Disutilities by bleed type were estimated based on differences in utilities reported during bleeds versus when having no bleeds, measured in patients with hemophilia A with inhibitors.[40,43] As stated above, bleed-associated disutilities for treated target joint bleeds and treated non-target joint bleeds were applied in full for two days, followed by an average of "No Bleed" and "Bleed" utilities for five days (Table 5.5).[40] In reality, bleed duration will vary depending on severity of the bleed, time to treatment, and other variables including location, so we have varied this assumption in a scenario analysis.

Table 5.5. Bleed-Related Disutilities

Bleed Disutilities	Value/Bleed/Cycle	Source
Bleed Not into a Target Joint	-0.002	Neufeld 2012
Target Joint Bleed	-0.003	Mazza 2016

These are based on a -0.16 and -0.28 disutility per day for treated bleed and treated joint bleed, respectively.

Economic Inputs

Drug utilization for factor VIII was based on a market basket approach using proportions of different types of factor VIII treatments seen in recent market basket data provided by the American Thrombosis and Hemostasis Networks (ATHN), representative treatments of each type, and typical doses for those products. Specifically, Advate® was selected to represent standard half-life treatment, used by 71.18 % of the patients, and Eloctate® was selected to represent extended half-life treatment, used by 28.82% of patients and doses of 118.2 IU/kg for Advate and 111.2 IU/kg for Eloctate were used based on average doses seen in ATHN data for first time prophylactic treatment regimens at the underlying US hemophilia treatment centers that provide data to the ATHN and which were also consistent with the labels, input from clinical experts, and a recently published economic models.[77-79] We also conduct a sensitivity analysis using doses consistent with the clinical trial used in the NMA in the clinical section described further below. Dosing of these drugs varies by weight and in both model's patient weight by age was modeled based on average weight by age for males in the US. To estimate utilization during bleeds, given input from clinical experts that most patients treat bleeds with the same drug they are using for prophylaxis, the same market basket will be used but with doses for each drug consistent with treating bleeds.

Utilization of emicizumab was assumed to be the same as seen in HAVEN 3.[21] Utilization for valoctocogene roxaparvovec was the highest dose seen in the available trials, as that dose was associated with the largest treatment effects across time (Table 5.6).

For valoctocogene roxaparvovec, a dose of $6x10^{13}$ vg/kg was used which has been found to have the best efficacy in available trials. For emicizumab, 3 mg/kg every week for the first month and then 3 mg/kg every other week after the first month was used which is consistent with the best efficacy seen in the Haven 3 trial.[21] A lifetime treatment duration is assumed in each version of the model.

For treated bleeds and treated joint bleeds, factor VIII use was assumed to be 50.4 IU/kg per bleed and the same market basket was assumed.

Table 5.6. Treatment Regimen Dosage

Generic name	Drug A	Drug B	Drug C	Drug C
Brand Name	Hemlibra®	Roctavian™	Advate®	Eloctate®
Generic Name	Emicizumab	Valoctocogene roxaparvovec	Antihemophilic factor (recombinant)	Antihemophilic factor (recombinant), Fc fusion protein
Manufacturer	Genentech	BioMarin	Baxter	Biogen
Route of Administration	subcutaneous	IV	IV	IV
Dosing	3 mg/kg every week for the first month and then 3 mg/kg every 2 weeks after	$6x10^{13}$ vg/kg	118.2 IU/kg every week	111.2 IU/kg every week

For emicizumab and the factor VIII products we recognize that there are different dosing regimens and any that use the same amount would conform to our results.
IV: intravenous

Drug Costs

As valoctocogene roxaparvovec has not been approved, no WAC or net price estimates are available. We therefore conducted the base-case analysis using a placeholder price of $2,500,000, based on statements from the manufacturer indicating consideration of prices of around $2 million to $3 million per treatment.[80] In the absence of data on usual discounts for gene therapy, we assumed no discounting and used this placeholder for the net price of this treatment. For the other drugs in this analysis, we derived net prices from average sales prices (ASP) to calculate treatment-related health care costs, as we did not have other data on net prices that included discounts/rebates for these agents.[81] Based on the regimen dosage specified in Table 5.6 and available formulations for each drug, the model will utilize the lowest-cost combination of vials for each regimen. Further, available prices were adjusted by removing the portion of costs associated with a furnishing fee and add on costs. This involved a 45 cents reduction per mg and a six percent deduction for emicizumab and a 23-cent reduction per IU for the factor VIII products along with a six percent deduction (see Table 5.7).

Table 5.7. Drug Costs at Base-Case Doses for an 18-Year-Old Patient

Drug	WAC per Dose	Discount from WAC*	Add-On Discount	Net Price per Dose†	Net Price per Year‡
Valoctocogene roxaparvovec (Roctavian™)	$2,500,000#	--	0%	$2,500,000#	Not applicable
Emicizumab§ (Hemlibra®)	$100.19/mg	4.7%	6%	$89.33/mg	$569,105
Antihemophilic Factor (recombinant) (Advate®)	$1.69/IU	18.6%	6%	$1.08/IU	$542,539
Antihemophilic Factor (recombinant), Fc fusion protein (Eloctate®)	$2.23/IU	3.2%	6%	$1.82/IU	$858,026

*Calculated from WAC and ASP

†Net price from July 2020 ASP Pricing File, available at: https://www.cms.gov/medicare/medicare-part-b-drug-average-sales-price/2020-asp-drug-pricing-files, accessed June 30, 2020. From those numbers $0.23/IU for each factor VIII drug and $0.45 per mg for emicizumab was subtracted along with 6% of the remaining costs to adjust for the portion of costs made up by furnishing fees that would not generally apply.

‡Assume weight is 81.4kg for the average 18-year-old male

§Maintenance dose

#Placeholder price for valoctocogene roxaparvovec

Treatment Cost Per Bleed

Based on the market basket described above (71.18% standard half-life, and 28.82% extended half-life) at a dose of 54 IU/kg per bleed and using the costs described above in Table 5.7, the treatment-related costs of a bleed are $5,275 for an 81.4 kg male.

Non-Drug Costs

Health State Costs

Non-pharmacological costs from Shrestha et al. were used to inform the direct non-pharmacy related medical costs associated with treated bleeds and treated joint bleeds (see Table 5.8). The model purposely uses per-bleed costs here to focus on cost reductions associated with reductions in bleeds. Some fixed costs, for example those associated with diagnosis of hemophilia A, are ignored in the model knowing that they would likely be the same across treatments and would not affect incremental cost ratios. Estimates of these costs were available for three age groups: < 18, 18 to 45, and > 45 years old. Shrestha et al. examined mostly patients not on prophylactic treatment, and the costs per bleed generally were not statistically significantly different for those on prophylaxis. However, the study found statistically significantly lower costs for patients under the age of 18 on prophylaxis and the estimated reduction was included for those patients in the model.[82]

Table 5.8. Non-Drug Costs per Bleed by Age

Age (years)	Cost	Source
< 18	$765.48	Shrestha 2017
18-45	$4,604.32	Shrestha 2017
> 45	$6,858.24	Shrestha 2017

Added Cost of Arthropathy

In addition to the per-bleed costs, published findings of increased utilization associated with arthropathy were incorporated into the model. Specifically, reported differences in annual use of outpatient physician visits, outpatient nurse visits, as well as joint-related tests including X-ray and magnetic resonance imaging were used along with CMS physician fee schedule costs for 2018, inflated to 2019 (see Table 5.9).[83,84]

Table 5.9. Utilization Related Cost Differences of Arthropathy versus No Arthropathy

	Annual Cost	Source
No Arthropathy	$354.20 per cycle based on office visits and joint related tests	O'Hara 2018 and CMS Fees
Arthropathy	$618.28 per cycle based on office visits and joint related tests	O'Hara 2018 and CMS Fees
Surgery	Arthropathy cost plus $44,717.17*	Earnshaw 2015

*The cost of surgery was derived from Earnshaw et al., which reported a surgery cost of $44,717.17 when inflated to 2019 dollars.[44]

Societal Costs

Costs associated with lost time from work for patients and caregivers were estimated based on a burden of illness analysis by Zhou et al.[45] The costs were inflated from 2011 to 2019 by using the total compensation per hour for civilian workers from the Bureau of Labor Statistics. The calculated cost per treated bleed was $1,162.28.

Equal Value Life Years Gained

Because the model assumed no differential mortality effect of prophylaxis options for hemophilia A in patients without inhibitors, an analysis of equal value life years gained (evLYG) would be identical to the costs per QALY projected by the model. Hence, these were not included separately here.

Sensitivity Analyses

We ran one-way sensitivity analyses to identify the key drivers of model outcomes, using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges (+/- 25%) for each input described in the model inputs section above to evaluate changes in incremental costs and in

incremental QALYs for valoctocogene roxaparvovec, at its placeholder price, in model 1 and emicizumab versus factor VIII in model 2. Probabilistic sensitivity analyses for each model were also performed by jointly varying all model parameters over 10,000 simulations. The selected distributions for the inputs can be found in Table E2 in Appendix E. From the probabilistic sensitivity analyses we generated acceptability curves showing the percent of simulations where the treatment in question is deemed cost effective relative to the comparator at various levels of willingness to pay for QALYs.

Scenario Analyses

The scenario analyses included the following:

- Extending duration of disutility from bleeds to 7 full days from 2 full days and 5 half days.
- Doubling the bleed rates for patients with arthropathy across all treatments.
- Including societal costs beyond the health care sector
- A scenario where patients begin valoctocogene roxaparvovec at the age of 40 and with a PS of 20 (Model 1 only).
- Scenarios in each version of the model where surgery returns patients to a PS of 13

In addition, we conducted NMA-related scenario analyses in both models using the dose for standard half-life factor VIII seen in the trial from which the efficacy estimates in the NMA described in the clinical section above were derived, and where the use of extended half-life factor VIII was estimated based on clinical opinion of equivalence as well as the drug label for Eloctate.[21,77,78] Specifically factor VIII prophylaxis with Advate and Eloctate used doses of 80 IU/kg every week and 78 IU/kg every week, respectively. For these analyses, efficacy estimates from the NMA were also incorporated to project bleed rates in the factor VIII arms of the models. Relative rates of treated bleeds and treated joint bleeds from the combined regimen ICER NMA involving emicizumab and factor VIII treatments combined with the treated bleeds and treated joint bleeds for emicizumab were used to determine the rates of treated bleeds and treated joint bleeds for factor VIII. The ratio of treated target joint bleeds to treated joint bleeds seen in Group B of the HAVEN 3 trial was used to estimate treated target joint bleeds from the number of treated joint bleeds for factor VIII. In addition, the ratio of all bleeds to treated bleeds seen in Group B of the HAVEN 3 trial was used to estimate total bleeds for factor VIII. An average of the ratios of all bleeds that were joint bleeds in all the arms of the HAVEN 3 as well as that seen in the POTTER trial were used to estimate total joint bleeds from treated bleeds for emicizumab and factor VIII.[21,36]

As valoctocogene roxaparvovec falls under ICER's SST framework, we conducted further scenario analyses as follows:

1. 50/50 shared savings in which 50% of lifetime health care net cost savings from a new treatment are assigned to the health care system instead of being assigned entirely to the new treatment. Further, the cost savings will be zero following the full switch in treatment.

2. Cost savings cap in which health care net cost savings generated by a new treatment are capped at $150,000 per year but are otherwise assigned entirely to the new treatment. Further, the cost savings will be zero following the full switch in treatment.

3. 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) to estimate projected trends in factor level decline.

4. Threshold analysis for duration of effect in patients receiving short-term benefit that would be needed to achieve cost-effectiveness thresholds.

5. The impact of an outcomes-based payment proposal for valoctocogene roxaparvovec where patients who do not respond to the treatment do not have to pay. Specifically, for patients meeting the following three conditions full reimbursement would be made: FVIII activity level is $\leq$ 5 IU/dL as measured by one stage assay; $\geq$2 spontaneous bleeds and/or one life-threatening spontaneous bleed in 6 months; and a return to continuous prophylactic FVIII products or emicizumab. To evaluate this scenario, we used trial results on factor levels adjusting for a small portion of patients that were deemed as non-responsive in the trials. This resulted in a higher projected starting point in factor levels, which we then modeled using the base-case approach for projecting declines across time in factor levels as well as the resulting number of bleeds per cycle. This also involved the same assumptions of patients eventually switching to emicizumab as described in the base case for version 1 of the model above.

Threshold Analyses

With the base-case models, we performed threshold analyses to estimate the maximum prices of valoctocogene roxaparvovec and emicizumab that would correspond to a range of incremental cost-effectiveness ratios ($50,000, $100,000, $150,000, and $200,000 per QALY).

For each of the SST scenario analyses in model 1, we also explored threshold prices corresponding to willingness to pay thresholds of $50,000, $100,000, $150,000, and $200,000 per QALY.

5.3 Results

Treatment Duration Projections for Model 1

Table 5.10 below shows the projected factor levels and associated bleeds for valoctocogene roxaparvovec for the base case, as well as for the optimistic and conservative scenarios used in the SST scenario analyses.

Table 5.10. Projected Factor Levels and Treated Joint Bleeds for Valoctocogene Roxaparvovec

Cycle	Base Case Factor Level	Base Case Bleeds	Optimistic Factor Level	Optimistic Bleeds	Conservative Factor Level	Conservative Bleeds
1	Start	Half of Factor VIII	Start	Half of Factor VIII	Start	Half of Factor VIII
2	64	0	89	0	64	0
3	49	0.156	68	0	49	0.156
4	33	0.156	46	0.156	33	0.156
5	27	0.156	38	0.156	27	0.156
6	22	0.156	30	0.156	22	0.156
7	19	0.156	27	0.156	19	0.156
8	17	0.156	23	0.156	17	0.156
9	14	0.156	20	0.156	14	0.156
10	12	0.156	18	0.156	12	0.156
11	10	0.48	16	0.156	9	0.67
12	8	0.76	14	0.156	7	0.8
13	7	0.8	12	0.156	4	1.42*
14	6	0.8	10	0.48	1	2.52*
15	5	0.91	9	0.67	< 1	Switch
16	4	1.42*	8	0.76		
17	4	1.42*	7	0.8		
18	3	2.52*	6	0.8		
19	3	2.52*	5	0.91		
20	2	2.52*	5	0.91		
21	2	2.52*	4	1.42*		
22	2	2.52*	4	1.42*		
23	1	2.52*	3	2.52*		
24	1	2.52*	3	2.52*		
25	<1	Switch	2	2.52*		
26			2	2.52*		
27			2	2.52*		
28			2	2.52*		
29			1	2.52*		
30			1	2.52*		
31			1	2.52*		
32			<1	Switch		

*At projected factor levels less than 5, patients had 5% emicizumab and 95% valoctocogene roxaparvovec. Bleed rates by factor level were estimated based on a normalized set of bleeds per factor level based on a 2011 study.[35] Each cycle duration is six months.

Base-Case Results

Table 5.11 describes the discounted lifetime total costs and outcomes from Model 1. In the base-case analysis, valoctocogene roxaparvovec, at its placeholder price, is projected to have lower total costs, lower bleeds, and more QALYs associated with it. The table also includes the projected discounted total number of factor VIII infusions associated with each regimen.

Table 5.11. Results for the Base-Case Model Comparing Valoctocogene Roxaparvovec to Factor VIII in Adults*

Treatment	Drug Cost	Total Cost	Infusions	Joint Bleeds	Treated Non-Target Joint Bleeds	Treated Target Joint Bleeds	Life Years	QALYs
Factor VIII (Model version1 – Health Sector Perspective)	$18,269,000	$18,722,000	3705.17	68.97	15.92	18.57	26.53	19.087
Valoctocogene Roxaparvovec (Model version 1 – Health Sector Perspective)	$13,293,000	$13,693,000	31.11	43.70	15.28	17.83	26.53	19.091

QALY: quality-adjusted life year

*Results use a placeholder price of $2,500,000 for valoctocogene roxaparvovec

Table 5.12 describes the discounted lifetime total costs and outcomes from Model 2. Emicizumab is projected to have lower costs with the same projected number of bleeds and quality adjusted life years. The table also includes the projected discounted total number of factor VIII infusions associated with each regimen.

Table 5.12. Results for the Base-Case Model Comparing Emicizumab to Factor VIII for All Patients

Treatment	Drug Cost	Total Cost	Infusions	Joint Bleeds	Treated Non-Target Joint Bleeds	Treated Target Joint Bleeds	Life Years	QALYs
Factor VIII (Model version 2 – Health Sector Perspective)	$14,821,000	$15,104,000	4058.67	38.60	12.64	13.76	29.14	24.141
Emicizumab (Model version 2 – Health Sector Perspective)	$13,316,000	$13,598,000	26.41	38.60	12.64	13.76	29.14	24.141

QALY: quality-adjusted life year

Table 5.13 describes the incremental cost and QALY results from the first model based on the base-case costs and QALYs shown above. In Model 1, valoctocogene roxaparvovec at its placeholder price was a dominant treatment.

Table 5.13. Incremental Cost-Effectiveness Ratios for the Base Case of Model 1*

Treatment	Incremental Cost	Incremental QALYs	Incremental Cost-Effectiveness Ratio
Factor VIII (Model version 1 – Health Sector Perspective)	Reference	Reference	Reference
Valoctocogene Roxaparvovec (Model version 1 – Health Sector Perspective)	-$4,988,000	0.004	Dominant

QALY: quality-adjusted life year

*Results use a placeholder price of $2,500,000 for valoctocogene roxaparvovec

Table 5.14 below shows the incremental base case results for Model 2. Emicizumab was found to be highly cost saving with equal projected QALYs.

Table 5.14. Incremental Cost-Effectiveness Ratios for the Base Case of Model 2

Treatment	Incremental Cost	Incremental QALYs	Incremental Cost-Effectiveness Ratio
Factor VIII (Model version 2 – Health Sector Perspective)	Reference	Reference	Reference
Emicizumab (Model version 2 – Health Sector Perspective)	-$1,505,000	0.000	Cost Saving

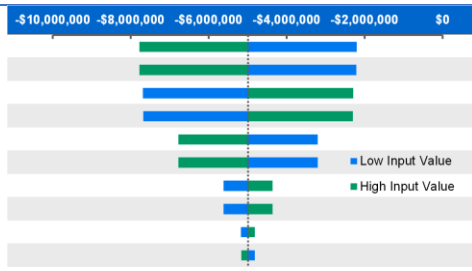
QALY: quality-adjusted life year

Sensitivity Analysis Results

Figure 5.2 below illustrates the one-way sensitivity analyses for model 1. The drug costs and prophylactic drug dosing for the factor VIII products have a substantial influence on the projected incremental costs. The net drug cost of emicizumab and its dose were also key drivers, as patients beginning on valoctocogene roxaparvovec end up switching to emicizumab once projected factor levels become too low. However, the incremental costs remain negative across a wide range of those values. The projected incremental QALYs in model 1 are highly sensitive to changes in bleed rates associated with the particular treatments involved and somewhat sensitive to the utilities associated with various PS in both models. The number of days per bleed has some influence on the incremental QALYs in model 1.

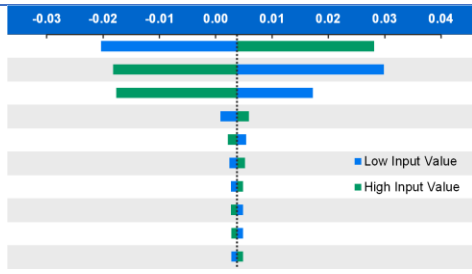
Figure 5.2. Tornado Diagrams for One-Way Sensitivity Analyses of Valoctocogene Roxaparvovec versus Factor VIII*

Model 1 Health Sector - Valrox Incremental Costs



Parameter	Low Input Value	High Input Value
Advate (F8) Net Drug Cost	$0.86	$1.44
Advate (F8) Prophylaxis Drug Dosing	88.65	147.75
Emicizumab Net Drug Cost	$71.27	$118.79
Emicizumab (Month 2+) Prophylaxis Drug Dosing	1.13	1.88
Eloctate (F8) Net Drug Cost	$1.45	$2.42
Eloctate (F8) Prophylaxis Drug Dosing	83.40	139.00
Valactogene Net Drug Cost	$1,875,000.00	$3,125,000.00
Valactogene Prophylaxis Drug Dosing	0.75	1.25
Advate (F8) Furnishing Discount (%)	4.50%	7.50%
Emicizumab Furnishing Discount (%)	0.05	0.08

Model 1 - Valrox Incremental QALYs



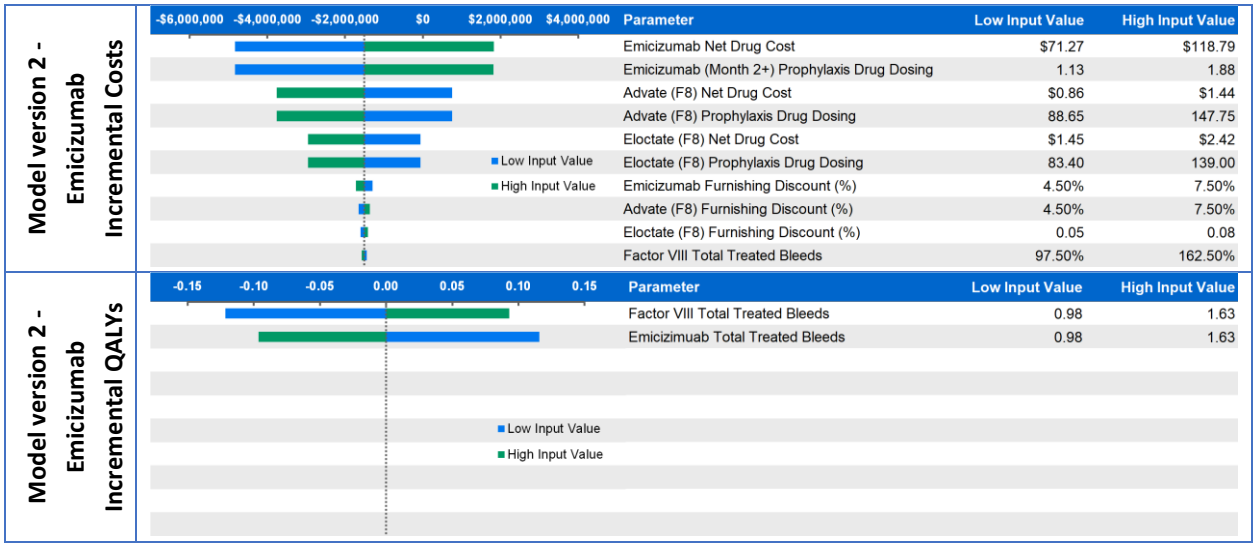
Parameter	Low Input Value	High Input Value
Factor VIII Total Treated Bleeds	0.98	1.63
Emicizimuab Total Treated Bleeds	0.98	1.63
Valacocogene Treated Joint Bleed RR	0.09	0.30
Average Number of Blood Days	1.00	7.00
Pettersson 13-21 Utilities (Age > 60)	0.41	0.68
Pettersson 22-28 Utilities (Age > 60)	0.41	0.68
Pettersson 13-21 Utilities (30 < Age ≤ 40)	0.56	0.93
Pettersson 22-28 Utilities (30 < Age ≤ 40)	0.56	0.93
Pettersson 13-21 Utilities (50 < Age ≤ 60)	0.47	0.79
Pettersson 22-28 Utilities (50 < Age ≤ 60)	0.47	0.79

QALY: quality-adjusted life year

*Results use a placeholder price of $2,500,000 for valoctocogene roxaparvovec

Figure 5.3 below shows the one-way sensitivity analysis results for model 2. The cost and dose of emicizumab had substantial influence on costs. In addition, the drug costs and prophylactic drug dosing of factor VIII have a substantial influence on the projected incremental costs. In addition, there are ranges of costs and dosing where the incremental cost of emicizumab relative to factor VIII becomes positive. The projected incremental QALYs are highly sensitive to efficacy measures of emicizumab and factor VIII but are not sensitive to other variables because of having the same bleed rates.

Figure 5.3 Tornado Diagrams for One-Way Sensitivity Analyses of Emicizumab versus Factor VIII



QALY: quality-adjusted life year

Table 5.15 summarizes the probabilistic sensitivity analyses showing the percent of simulations that project cost effectiveness for valoctocogene roxaparvovec relative to factor VIII at various standard thresholds for cost effectiveness. Though dominant in the base case, there are nearly 6% of simulations where factor VIII becomes cost effective at various thresholds. The 95% credible intervals and ranges can be found in the appendix Table E4.

Table 5.15. Probabilistic Sensitivity Analysis Results: Valoctocogene Roxaparvovec versus Factor VIII*

	Cost Effective at $50,000 per QALY	Cost Effective at $100,000 per QALY	Cost Effective at $150,000 per QALY	Cost Effective at $200,000 per QALY	Cost Effective at $250,000 per QALY
Valoctocogene Roxaparvovec (Model version 1 – Health Sector Perspective)	93.92%	93.93%	93.93%	93.93%	93.93%

QALY: Quality-adjusted life year

*Results use a placeholder price of $2,500,000 for valoctocogene roxaparvovec

Table 5.16 summarizes the probabilistic sensitivity analyses showing the percent of simulations that project cost effectiveness for emicizumab relative to factor VIII at various standard thresholds for cost effectiveness. Despite being highly cost saving with equal efficacy in the base case, in over 30% of the simulations at each of the selected threshold levels emicizumab is found to not be cost effective. These results show that several of the inputs have both sufficient potential variance and influence on the first version of the model that in roughly 30% of the simulations there are potential

sets of inputs that would give a different conclusion than that seen in the base case. The 95% credible intervals and ranges can be found in the appendix Table E4.

Table 5.16. Probabilistic Sensitivity Analysis Results: Emicizumab versus Factor VIII

	Cost Effective at $50,000 per QALY	Cost Effective at $100,000 per QALY	Cost Effective at $150,000 per QALY	Cost Effective at $200,000 per QALY	Cost Effective at $250,000 per QALY
Emicizumab (Model version 2)	69.43%	69.43%	69.42%	69.46%	60.47%

QALY: quality-adjusted life year

Scenario Analyses Results

Table 5.17 summarizes the results from the scenario analyses using the doses of factor VIII used in the base-case versions. In each of the scenarios applied to Model 1, valoctocogene roxaparvovec, at its placeholder price, was found to be a dominant treatment.

Table 5.17. Scenario Analyses for Model 1*

Scenario	Treatment	Incremental Cost	Incremental QALYs	Incremental Cost-Effectiveness Ratio
Higher Bleed Duration	Valoctocogene Roxaparvovec	-$4,988,000	0.006	Dominant
Higher Bleed Rates	Valoctocogene Roxaparvovec	-$5,001,000	0.008	Dominant
Societal Perspective	Valoctocogene Roxaparvovec	-$4,990,000	0.004	Dominant
Older Age (40) and Pettersson Score (20) Start	Valoctocogene Roxaparvovec	-$4,866,000	0.005	Dominant
Pettersson Score Return to 13	Valoctocogene Roxaparvovec	-$4,988,000	0.004	Dominant

*Results use a placeholder price of $2,500,000 for valoctocogene roxaparvovec
QALY: quality-adjusted life year

Table 5.18 shows the scenario analyses for model 2. Across all scenarios, emicizumab remains a cost saving treatment with equal efficacy.

Table 5.18. Scenario Analyses for Model 2

Scenario	Treatment	Incremental Cost	Incremental QALYs	Incremental Cost-Effectiveness Ratio
Higher Bleed Duration	Emicizumab	-$1,505,000	0.000	Cost Savings
Higher Bleed Rates	Emicizumab	-$1,505,000	0.000	Cost Savings
Societal Perspective	Emicizumab	-$1,505,000	0.000	Cost-Savings
Return to PS 13	Emicizumab	-$1,505,000	0.000	Cost Savings

QALY: quality-adjusted life year

Table 5.19 below shows the incremental cost and QALY results from the two SST cost-savings scenarios. In the scenario where savings are cut in half, valoctocogene roxaparvovec remained dominant, as the incremental cost was still negative. In the scenario that capped savings at $150,000 per year, however, incremental cost rose to $923,000, resulting in an estimated cost effectiveness ratio greater than $230 million per QALY. We recommend an emphasis on interpretation of the threshold-based prices shown below due to the small differences and uncertainty in the incremental QALYs. Incremental cost and QALY results for the other SST scenarios are shown in Appendix E; valoctocogene roxaparvovec remained dominant in each.

Table 5.19. Incremental Costs and QALYs in the SST Cost-Savings Scenario Analyses

Scenario	Model Version	Treatment	Incremental Cost	Incremental QALYs	Incremental Cost-Effectiveness Ratio
Half Savings During Treatment	Health Sector	Valoctocogene Roxaparvovec	-$666,000	0.004	Dominant
Cap Savings at $150,000/Year During Treatment	Health Sector	Valoctocogene Roxaparvovec	$923,000	0.004	$230,750,000/QALY

QALY: quality-adjusted life year

Threshold Analyses Results

Base-Case Model

Table 5.20 shows threshold prices that would result in cost-effectiveness ratios of $50,000, $100,000, $150,000, and $200,000 per QALY for the base-case versions of model 1. (Threshold prices do not appear to vary due to rounding.) As mentioned above, because the model assumed no differential mortality effect of prophylaxis options for hemophilia A in patients without inhibitors, threshold analysis results for equal value life years gained (evLYG) would be identical to those for costs per QALY projected by the model.

Table 5.20. Threshold Analysis Results for the Base Case for Model 1*

Perspective	WAC per unit	Net Price per unit	Unit Price to Achieve $50,000 per QALY	Unit Price to Achieve $100,000 per QALY	Unit Price to Achieve $150,000 per QALY	Unit Price to Achieve $200,000 per QALY
Health Sector	$2,500,000	$2,500,000	$7,490,000	$7,490,000	$7,490,000	$7,490,000

*WAC and net prices for valoctocogene roxaparvovec are placeholder prices
QALY: quality-adjusted life year

Because the base case analysis of emicizumab found identical QALYs compared with factor VIII prophylaxis, it is not possible to calculate the usual threshold prices. In this situation, whichever therapy is less expensive (factor VIII was around 11% more expensive per year) would be preferred at all thresholds. Again, because the model assumed no differential mortality effect of prophylaxis options for hemophilia A in patients without inhibitors, threshold analysis results for equal value life years gained (evLYG) would be identical to those for costs per QALY projected by the model.

Threshold on Duration

As valoctocogene roxaparvovec was a dominant treatment, duration thresholds did not apply.

Threshold Prices in the SST Scenarios

Table 5.21 below shows threshold prices in the shared cost-savings scenarios in Model 1. Threshold prices were approximately $3.2 million in the scenario with half of the net cost-savings returned to society and approximately $1.6 million in the capped savings scenario where the cost savings was capped at $150,000 per year in present value.

Table 5.21. Threshold Analysis Results for the SST Shared Savings Scenarios in Model 1*

Perspective	WAC per unit	Net Price per unit	Unit Price to Achieve $50,000 per QALY	Unit Price to Achieve $100,000 per QALY	Unit Price to Achieve $150,000 per QALY	Unit Price to Achieve $200,000 per QALY
Health Sector Half Cost Savings*	$2,500,000	$2,500,000	$3,166,000	$3,166,000	$3,166,000	$3,166,000
Health Sector Capped Cost Savings ($150,000/yr)	$2,500,000	$2,500,000	$1,579,000	$1,581,000	$1,583,000	$1,585,000

*Results may not appear to differ across thresholds due to rounding.
QALY: quality-adjusted life year

Impact of Using Doses and Efficacy of Factor VIII Related to the NMA in the Clinical Section

In this NMA related set of scenario analyses a dose of 80 IU/kg is used for Advate and a dose of 78 IU/kg is used for Eloctate. In addition, bleed rates for the factor VIII products were generated using the NMA described in the clinical section above and proportional assumptions for types of bleeds as in the base case above (see Table 5.22 below).

Table 5.22. Annual Bleed Rates for Factor VIII in the NMA Scenario Analyses

Drug	All Bleeds	All Joint Bleeds	Treated Non-Target Joint Bleeds	Treated Target Joint Bleeds
Factor VIII	4.56	3.01	1.09	1.19

Table 5.23 describes the discounted lifetime total costs and outcomes for model 1. In the base-case analysis, valoctocogene roxaparvovec, at its placeholder price, is projected to have higher total costs, lower bleeds, and more QALYs associated with it.

Table 5.23. Results for the NMA Scenario Analysis Comparing Valoctocogene Roxaparvovec to Factor VIII in Adults*

Treatment (perspective)	Drug Cost	Total Cost	Joint Bleeds	Treated Non-Target Joint Bleeds	Treated Target Joint Bleeds	Life Years	QALYs
Factor VIII (Health Sector Perspective)	$12,540,000	$13,243,000	89.73	28.97	31.53	26.53	19.015
Valoctocogene Roxaparvovec (Health Sector Perspective)	$13,293,000	$13,694,000	43.13	15.06	17.56	26.53	19.092

*Results use a placeholder price of $2,500,000 for valoctocogene roxaparvovec

The results from this scenario in model 2 are shown in Table 5.24 below. Emicizumab was associated with higher total costs, lower bleeds, and higher QALYs from the health sector perspective.

Table 5.24. Results for the NMA Scenario Analysis Comparing Emicizumab to Factor VIII for All Patients

Treatment	Drug Cost	Total Cost	Joint Bleeds	Treated Non-Target Joint Bleeds	Treated Target Joint Bleeds	Life Years	QALYs
Factor VIII	$10,117,000	$10,650,000	76.78	23.07	23.37	29.14	23.858
Emicizumab	$13,316,000	$13,598,000	38.60	12.64	13.76	29.14	24.141

Table 5.25 describes the incremental cost and QALY results from model 1 based on the costs and QALYs shown above. In model 1, valoctocogene roxaparvovec, at its placeholder price, had an incremental cost effectiveness ratio of over $5M compared to factor VIII.

Table 5.25. Incremental Cost-Effectiveness Ratio for the NMA Scenario in Model 1*

Treatment (Perspective)	Incremental Cost	Incremental QALYs	Incremental Cost-Effectiveness Ratio
Factor VIII (Health Sector Perspective)	Reference	Reference	Reference
Valoctocogene Roxaparvovec (Health Sector Perspective)	$452,000	0.076	$5,949,000/QALY gained

*Results use a placeholder price of $2,500,000 for valoctocogene roxaparvovec

Table 5.26 describes the incremental costs and QALYs in model 2. Emicizumab was found to have an incremental cost effectiveness ratio of over $10 M per QALY relative to factor VIII.

Table 5.26. Incremental Cost-Effectiveness Ratio for the NMA Scenario in Model 2

Treatment	Incremental Cost	Incremental QALYs	Incremental Cost-Effectiveness Ratio
Factor VIII	Reference	Reference	Reference
Emicizumab	$2,948,000	0.284	$10,393,000/QALY gained

Model Validation

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report (and supplemental Appendix materials). We also conducted sensitivity analyses with null input values to ensure the model was producing findings consistent with expectations. Further, independent modelers tested the mathematical functions in the model as well as the specific inputs and corresponding outputs.

Model validation was also conducted in terms of comparisons to other model findings. We searched the literature to identify models that were similar to our analysis, with comparable populations, settings, perspective, and treatments.

Prior Economic Models

A 2018 ICER report reviewed hemophilia A individuals with inhibitors and included discussions regarding prior economic analyses.[85] Details on those economic analyses can be seen in that report.

Since the 2018 ICER report, there have been several related models published in the literature. Coppola et al. in 2017 focused on prophylaxis versus on demand treatment with factor VIII, based

on historical data for patients aged 12 and over in Italy. This model used annual cycles and tracked PS from 0-78 across time based on an increase in PS for every 6.52 bleeds for patients younger than 25 and by one for every 36.52 bleeds after the age of 25. Surgery is separately included in the model based on annual proportions of patients requiring surgery and is not attached nor does it impact PS in their model. The dose used for factor VIII prophylaxis was 75 IU/kg per week, close to the dose seen in the trial we used as our base case and their bleed rates at that dose were fairly similar to those in our model.

A recent manufacturer-sponsored study by Cook et al. in 2020 assessed the cost-effectiveness of valoctocogene roxaparvovec compared to those on Eloctate 40 IU/kg thrice weekly in patients with moderate and severe hemophilia A without inhibitors. Cook et al. used a microsimulation with weekly cycles to transition patients between four health states: no bleed, joint bleed, non-joint bleed, and dead. Patients start in the no bleed state and can either stay in the no bleed state or transition to the non-joint bleed or joint bleed states. The model separately tracks PS and patients transition to a higher PS after 12.6 joint bleeds regardless of age. Patients get surgery when they reach a PS of 28 and then every 20 years after that until they are 80 but can continue to experience higher PS based on bleeds. State-specific utilities and surgery costs were tied to an increased PS, which ranged from a score of 0 to 78. Efficacy of factor VIII in their model centered around an ABR rate of 5 for patients on Eloctate.

The Cook model has no association between treatment and mortality but does include a small impact of hemophilia on mortality. For those on valoctocogene roxaparvovec, Cook et al. used the factor VIII levels from the phase 3 clinical study to inform the transition probabilities for the first three years based on the mean annual bleed rates and the proportion of patients who are bleed-free. After three years, patients followed an individual-specific linear annual decline of factor VIII levels until they reached a level below 5 IU/dL at which the gene therapy was no longer considered effective. Those who no longer responded to valoctocogene roxaparvovec transitioned to the Eloctate arm. The linear projections of factor level decline had patients switch back to Eloctate when factor levels reached 5 IU/dL and led to an average successful duration of roughly 11 years. For the factor VIII prophylaxis arm in the Cook et al. model, patients were assigned to one of three bleed categories: (1) patients who experience bleeds with low frequency of 0-1 ABR; (2) moderate frequency bleeds of 1.7-5.0 ABR; and (3) high frequency bleeds of 6-22 ABR. 40% were assigned to category 1, 33% were assigned to category 2, and 27% were assigned to category 3. Lastly, it was assumed that patients above a factor VIII level of 15 IU/dL could not experience joint bleeds but could experience non-joint bleeds.

In addition to using a relatively high dose of Eloctate, and using only Eloctate, in the model they used a relatively high cost of $1.63 per IU. They also used a cost for valoctocogene roxaparvovec of $2,000,000, and a cost of surgery of $40,560. The utility scores in the Cook model associated with bleeds and the duration for bleeds were similar to our model; however, their model incorporated a separate disutility of factor VIII infusions of 0.0004 per infusion. In addition, surgery-related utility

as well as the utilities across PS were somewhat different, and declined across levels of PS all the way to 78. Overall, their model found more cost savings and slightly higher QALY gains associated with valoctocogene roxaparvovec than our model, but was consistent in terms of finding the treatment dominant. Most of the difference in the incremental utility results are because of the disutility used for infusions, and most of the cost differences are related to the higher dose of Eloctate and higher cost per IU.

Another recently published study by Zhou et al. focuses on the comparison between emicizumab and prophylaxis with factor VIII in all patients with hemophilia A. The Zhou et al. model used weekly cycles and had health states based on PS, where patients increased their PS every 12.6 joint bleeds and had surgery when their PS reached 28, at which point they returned to a PS of 1. The Zhou et. al paper also featured a certain portion of patients developing inhibitors depending on exposure to factor VIII, with 50% of patients developing inhibitors treated with emicizumab and 50% with BPA. The Zhou et al. paper used only Advate as a representative treatment for patients on factor VIII, with a weekly dose of 105 IU/kg and a cost of $1.58 per IU. Emicizumab was modeled using a cost of $99.20 per mg and a dose of 1.5 mg/kg weekly. The efficacy of emicizumab versus factor VIII in patients without inhibitors was based on HAVEN 3 and the relative risk of emicizumab in those patients was roughly 0.33, as opposed to the roughly 0.5 in our model. Overall, the treatment costs were higher and the relative efficacy of emicizumab was higher. Their analysis projected overall costs for a combination of patients with and without inhibitors, and estimated greater cost savings than our model. Much of the difference is related to the inclusion of patients with inhibitors but the differences in drug costs and dose of factor VIII are also important. At the doses for factor VIII used in the Zhou et al. analysis, a similar conclusion of cost reduction associated with emicizumab would be projected in our model with only those patients without inhibitors, but their model would project larger savings and larger reductions in bleeds. The Zhou et al. model did not include utilities or projections of QALYs.

Uncertainty and Controversies

The bleed rates for valoctocogene roxaparvovec were based on a very small number of patients and had to be projected over time. Hence actual bleed rates in patients taking this drug may vary from the model projections. We conducted scenario analyses to help assess potential variance, but all of the estimates inherently depend on results from a small population with imperfect follow up. Further, the bleed rates were estimated based on past findings relating factor levels in patients and bleeds. It is possible, though unknown, that valoctocogene roxaparvovec patients may have different bleed rates for a given factor level than that seen in the hemophilia A population generally. Adherence to factor VIII was not incorporated into the model. Likely it varies by age and treatment in the real world and could impact both costs and bleeds. However, adjusting for adherence in the model would be unlikely to change the main results here, especially if non-adherent patients ended up switching to emicizumab.

Dosing levels and efficacy for factor VIII were taken from patients in US treatment centers while those for emicizumab and valoctocogene roxaparvovec were from clinical trials. If those doses or efficacies are substantially different in practice it could change the results. In particular, given the methodology used in the study from which efficacy of factor VIII prophylaxis was estimated in the base case, we consider that we were using annual bleed rates that are likely lower than would have been found had the methodology of the emicizumab trials been used to determine the occurrence of bleeds. The sensitivity analyses provide some insight into potential changes.

We did not assign a disutility to infusions for factor VIII as we found no reported evidence for that in the literature. We also did not incorporate inhibitor development into the model as we received conflicting clinical opinion about which regimen would lead to more inhibitor development and it has already been shown that emicizumab is a dominant treatment for patients with inhibitors. We did report the discounted sum of infusions in the factor VIII arms in the base case results.

Most importantly, the dose of factor VIII is a key driver in the models. When using doses for factor VIII derived from the underlying trial that was used to estimate efficacy in the model, factor VIII appears very cost effective compared with valoctocogene roxaparvovec, at its placeholder price, and emicizumab. However, when incorporating doses of factor VIII currently seen in the US, the model 1 projects that valoctocogene roxaparvovec, at its placeholder price, is dominant and model 2 finds emicizumab is highly cost saving.

Limitations

The relationship between joint bleeds and surgery is imperfect and the model assumes one joint requiring surgery at a time. This may undercount surgeries overall. To help address this, we examined the impact of varying some of the model assumptions around surgery and the impact was small.

Utility scores for bleeds came from patients with inhibitors and these may be different in patients without inhibitors. The portions of the sensitivity analyses related to utility scores can be used to help assess the potential changes associated with different utility decrements associated with bleeds.

We are using a placeholder price for valoctocogene roxaparvovec.

We use Advate and Eloctate as representative treatments and average doses from ATHN data. There are numerous other factor VIII products on the market and a wide variance of treatment regimens. The results here would not directly apply to those products and as shown in the sensitivity and scenario analyses variation in dosing can have major implications on the projected cost effectiveness of factor VIII.

5.4 Summary and Comment

In this analysis of valoctocogene roxaparvovec, now deemed preliminary due to issuance by the FDA of a complete response letter to its licensing application and using a placeholder price of $2.5 million, the therapy was found to be a dominant treatment for adult patients with hemophilia A without inhibitors when using doses of factor VIII typical of US patients at hemophilia treatment centers. This finding, however, varied in the sensitivity analyses and importantly valoctocogene roxaparvovec was not at all cost effective when the model incorporated doses of factor VIII and efficacy results from the trial used in the NMA reported in the clinical sections. In general, the QALY differences were small and the cost differences varied widely across different doses of factor VIII as well as in different savings scenarios for valoctocogene roxaparvovec relative to factor VIII.

Given that valoctocogene roxaparvovec meets ICER's criteria to be considered a high-impact single and short-term therapy (SST), we performed additional scenario analyses including two shared savings scenarios. These shared savings scenarios result in a range of cost-effectiveness threshold prices between $1.6 million and $3.2 million, lower than the base case threshold prices of approximately $7.5 million. The purpose of producing these alternative scenarios is to provide empirical findings that may stimulate public dialogue on the extent to which large cost savings should be incorporated in judgments of reasonable pricing for novel therapies that are delivered as single or short-term interventions.

The cost effectiveness of emicizumab in patients with hemophilia A without inhibitors was also highly dependent on what it is being compared to. The base-case analysis for emicizumab compared it to the average doses of factor VIII for prophylaxis as seen in the ATHN data set along with recent efficacy levels for factor VIII reported in the literature based on patients in US hemophilia treatment centers that we believe represent evidence based lower bounds on bleed rates for those treatments. At those dosing and efficacy levels, emicizumab was found to be a highly cost saving treatment with equal efficacy to factor VIII. However, at the lower doses of factor VIII seen in the trial used for the NMA reported in the clinical section and with relative efficacy based on that NMA, we found that emicizumab would not be cost effective relative to factor VIII at standard thresholds.

Overall, the findings illustrate that factor VIII is such an extremely costly treatment, especially at currently used dosages in the US, that new treatments are capable of generating large cost savings in comparison. If prices of factor VIII were to come down from effective competition or other measures, the appropriate pricing of new treatments, as suggested by cost-effectiveness thresholds, would come down significantly as well.

6. Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. We also recognize that there may be broader contextual issues related to the severity of the condition, whether other treatments are available, and ethical, legal, or other societal priorities that influence the relative value of illnesses and interventions. These general elements are listed in the table below, and the subsequent text provides detail about the elements that are applicable to the comparison of valoctocogene roxaparvovec to factor VIII prophylaxis and emicizumab to factor VIII prophylaxis. We sought input from stakeholders, including individual patients, patient advocacy organizations, clinicians, and manufacturers, to inform the contents of this section.

Each ICER review culminates in a public meeting of an independent voting Council of clinicians, patients, and health services researchers. As part of their deliberations, Council members will judge whether a treatment may substantially impact the considerations listed in Table 6.1. The presence of substantial other benefits or contextual considerations may shift a council member's vote on an intervention's long-term value for money to a different category than would be indicated by the clinical evidence and cost-effectiveness analyses alone. For example, a council member may initially consider a therapy with an incremental cost-effectiveness ratio of $150,000 per QALY to represent low long-term value for money. However, the Council member may vote for a higher value category if they consider the treatment to bring substantial other benefits or contextual considerations. Conversely, disadvantages associated with a treatment may lead a Council member to vote for a lower value category. A Council member may also determine that there are no other benefits or contextual considerations substantial enough to shift their vote. All factors that are considered in the voting process are outlined in ICER's value assessment framework, ultra-rare disease framework, and single and short-term therapy framework. The content of these deliberations is described in the last chapter of ICER's Final Evidence Report, which is released after the public meeting.

This section, as well as the Council's deliberation, provides stakeholders with information to inform their decisions on a range of issues, including shared decision-making between patients and clinicians, coverage policy development, and pricing negotiations.

Table 6.1. Categories of Potential Other Benefit and Contextual Considerations

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
Uncertainty or overly favorable model assumptions creates significant risk that base-case cost-effectiveness estimates are too optimistic.		Uncertainty or overly unfavorable model assumptions creates significant risk that base-case cost-effectiveness estimates are too pessimistic.
Very similar mechanism of action to that of other active treatments.		New mechanism of action compared to that of other active treatments.
Delivery mechanism or relative complexity of regimen likely to lead to much lower real-world adherence and worse outcomes relative to an active comparator than estimated from clinical trials.		Delivery mechanism or relative simplicity of regimen likely to result in much higher real-world adherence and better outcomes relative to an active comparator than estimated from clinical trials.
This intervention could reduce or preclude the potential effectiveness of future treatments.		This intervention offers the potential to increase access to future treatment that may be approved over the course of a patient's lifetime.
The intervention offers no special advantages to patients by virtue of presenting an option with a notably different balance or timing of risks and benefits.		The intervention offers special advantages to patients by virtue of presenting an option with a notably different balance or timing of risks and benefits.
This intervention will not differentially benefit a historically disadvantaged or underserved community.		This intervention will differentially benefit a historically disadvantaged or underserved community.
Small health loss without this treatment as measured by absolute QALY shortfall.		Substantial health loss without this treatment as measured by absolute QALY shortfall.
Small health loss without this treatment as measured by proportional QALY shortfall.		Substantial health loss without this treatment as measured by proportional QALY shortfall.
Will not significantly reduce the negative impact of the condition on family and caregivers vs. the comparator.		Will significantly reduce the negative impact of the condition on family and caregivers vs. the comparator.
Will not have a significant impact on improving return to work and/or overall productivity vs. the comparator.		Will have a significant impact on improving return to work and/or overall productivity vs. the comparator.
Other		Other

6.1 Potential Other Benefits and Contextual Considerations

Valoctocogene Roxaparvovec

Valoctocogene roxaparvovec is likely to somewhat improve productivity of patients with hemophilia A.

If valoctocogene roxaparvovec had been approved, it would have been the first gene therapy for hemophilia A. It is unlike any other therapies for hemophilia A that are currently available.

As discussed above, administration of factor VIII prophylaxis is burdensome. Gene therapy with valoctocogene roxaparvovec is a one-time therapy after which adherence is not required. Adherence to the therapy will be identical to that seen in clinical trials.

Gene therapy with valoctocogene roxaparvovec induces antibodies to AAV5. It is unclear whether a patient who has received valoctocogene roxaparvovec can ever receive another AAV5-based gene therapy or be retreated with valoctocogene roxaparvovec.

If valoctocogene roxaparvovec therapy is successful and generates several years of high levels of factor VIII, it could allow a patient to choose a period in life where they desire freedom from therapies for hemophilia. This could allow choices about education, career activities, travel, or sports that, though time-limited, might otherwise never be possible.

In resource-limited settings, particularly outside the US, there may be no availability of factor VIII for prophylaxis or treatment of bleeding. A person with severe hemophilia A treated with gene therapy could potentially live safely for years in such a setting, while without gene therapy they would be at risk of death from bleeding.

Emicizumab

Emicizumab is likely to somewhat improve productivity of patients with hemophilia A.

The mechanism of action of emicizumab is new for the treatment of patients with hemophilia A without inhibitors. As noted, it was initially introduced for the treatment of patients with hemophilia A with inhibitors.

Administration of emicizumab is substantially easier than administration of factor VIII as it is given by subcutaneous injection rather than intravenous infusion making it easier and quicker to administer. It is also administered much less frequently than factor VIII. It is likely that this will improve adherence, result in some patients choosing prophylaxis who were previously only willing to use on-demand therapy, and somewhat enhance flexibility in choices around work, education, physical activity, and geographic mobility. Additionally, in infants and young children

administration of factor VIII may require an implanted port that can result in complications such as infections and clotting. Adherence to emicizumab is likely to more closely approximate that seen in clinical trials than adherence to factor VIII prophylaxis.

Emicizumab is likely to reduce the burden on parents and caregivers of young children with hemophilia A.

Hemophilia

As discussed in ICER's 2018 report, many patients with hemophilia who were alive in the late 1970s and early-through-mid 1980s were infected with HIV and died, and others were infected with hepatitis C and have now developed cirrhosis and its complications, further complicating their management of the condition. These infections were due to contamination of the medical therapies (factor replacement therapies) the patients were administered. Patient groups that have suffered prior iatrogenic harm may be due special consideration as newer therapies become available.

QALY Shortfalls

One important contextual consideration to consider is the argument that society should give preference to treatments for patients with more severe conditions[86], and that giving priority to treatments according to "lifetime burden of illness" or "need" best represents the ethical instincts of a society or other decision-makers.[87,88] To inform this contextual consideration, ICER provides empirical results for the absolute QALY shortfall and proportional QALY shortfall. The absolute QALY shortfall is defined as the total absolute amount of future health patients with a condition are expected to lose without the treatment that is being assessed.[89] The ethical consequences of using absolute QALY shortfall to prioritize treatments is that conditions that cause early death or that have very serious lifelong effects on quality of life receive the greatest prioritization. Thus, certain kinds of treatments, such as treatments for rapidly fatal conditions of children, or for lifelong disabling conditions, score highest on the scale of absolute QALY shortfall.

The proportional QALY shortfall is measured by calculating the proportion of the total QALYs of remaining life expectancy that would be lost due to untreated illness.[90,91] The proportional QALY shortfall reflects the ethical instinct to prioritize treatments for patients whose illness would rob them of a large percentage of their expected remaining lifetime. As with absolute QALY shortfall, rapidly fatal conditions of childhood have high proportional QALY shortfalls, but the highest numbers can also often arise from severe conditions among the elderly who may have only a few years left of average life expectancy but would lose much of that to the illness without treatment.

For this population of hemophilia A patients without inhibitors, the absolute shortfall was estimated to be 13.3 QALYs, with a proportional shortfall of 0.26, representing a loss of 26% of total quality-adjusted life expectancy (QALE) without the condition. (Note that this estimate is impacted

by our assumption that there is no mortality effect from prophylaxis for hemophilia A in patients without inhibitors.) To provide some anchoring of these results, we also present a league table of absolute and proportional QALY shortfalls for a variety of conditions from prior ICER reports (Table 6.2), using a burden of disease calculator developed by Dutch investigators (https://imta.shinyapps.io/iDBC/) that allows for calculation of absolute and proportional QALY shortfalls under different assumptions.[88]

Table 6.2. League Table of Absolute and Proportional QALY Shortfalls for Selected Conditions

	From ICER reports			From iDBC tool[92]	
Condition	Age	% Male	Total Undiscounted QALYs with Standard of Care	Absolute Shortfall	Proportional Shortfall
Hemophilia A	18	100	38.6	13.3	0.26
Secondary Progressive Multiple Sclerosis	48	39	3.0	24.5	0.89
Treatment-resistant Major Depression	46	33	20.5	8.7	0.30
Cystic Fibrosis	2	52	25.8	42.3	0.62

QALY: quality-adjusted life year

7. Health Benefit Price Benchmarks

The health benefit price benchmark (HBPB) is a price range suggesting the highest price a manufacturer should charge for a treatment, based on the amount of improvement in overall health patients receive from that treatment, when a higher price would cause disproportionately greater losses in health among other patients due to rising overall costs of health care and health insurance. In short, it is the top price range at which a health system can reward innovation and better health for patients without doing more harm than good.

Health benefit price benchmarks were not calculated for emicizumab for this population of hemophilia patients without inhibitors, as treatment at the current price compared with factor VIII is projected to be cost-saving and produce at least as many QALYs. Additionally, unless indication specific pricing occurred, the HBPB for emicizumab should include its use in patients with inhibitors.

Given the FDA decision to issue a CRL for valoctocogene roxaparvovec, ICER is also not presenting health benefit price benchmarks for valoctocogene roxaparvovec in the Evidence Report.

8. Potential Budget Impact

Given the FDA decision to issue a CRL for valoctocogene roxaparvovec, ICER is not presenting a potential budget impact analysis for valoctocogene roxaparvovec. Emicizumab already has an established presence in the market and so no potential budget impact analysis is included for emicizumab.

9. Summary of the Votes and Considerations for Policy

9.1 About the New England CEPAC Process

During New England CEPAC public meetings, the New England CEPAC Council deliberates and votes on key questions related to the systematic review of the clinical evidence, an economic analysis of the applications of treatments under examination, and the supplementary information presented. Council members are not pre-selected based on the topic being addressed and are intentionally selected to represent a range of expertise and diverse perspectives.

Acknowledging that any judgment of evidence is strengthened by real-life clinical and patient perspectives, subject matter experts are recruited for each meeting topic and provide input to New England CEPAC Council members before the meeting to help clarify their understanding of the different interventions being analyzed in the evidence review. The same clinical experts serve as a resource to the New England CEPAC Council during their deliberation, and help to shape recommendations on ways the evidence can apply to policy and practice.

After the New England CEPAC Council votes, a policy roundtable discussion is held with the New England CEPAC Council, clinical experts, patient advocates, payers, and when feasible, manufacturers. The goal of this discussion is to bring stakeholders together to apply the evidence to guide patient education, clinical practice, and coverage and public policies. Participants on policy roundtables are selected for their expertise on the specific meeting topic, are different for each meeting, and do not vote on any questions.

At the October 30, 2020 meeting, the New England CEPAC discussed issues regarding the application of the available evidence to help patients, clinicians, and payers address important questions related to the use of emicizumab and valoctocogene roxaparvovec for hemophilia A. Following the evidence presentation and public comments (public comments from the meeting can be accessed here: https://www.youtube.com/watch?v=W96WyPk4gC0&feature=youtu.be) the New England CEPAC Council voted on key questions concerning the comparative clinical effectiveness, comparative value, and potential other benefits and contextual considerations related to emicizumab. These questions are developed by the ICER research team for each assessment to ensure that the questions are framed to address the issues that are most important in applying the evidence to support clinical practice, medical policy decisions, and patient decision-making. The voting results are presented below, along with specific considerations mentioned by New England CEPAC Council members during the voting process.

In its deliberations and votes related to value, the New England CEPAC Council considered the individual patient benefits, and incremental costs to achieve such benefits, from a given intervention over the long term.

There are four elements to consider when deliberating on long-term value for money (see Figure 9.1 below):

1. Comparative clinical effectiveness is a judgment of the overall difference in clinical outcomes between two interventions (or between an intervention and placebo), tempered by the level of certainty possible given the strengths and weaknesses of the body of evidence. The New England CEPAC Council uses the ICER Evidence Rating Matrix as its conceptual framework for considering comparative clinical effectiveness.

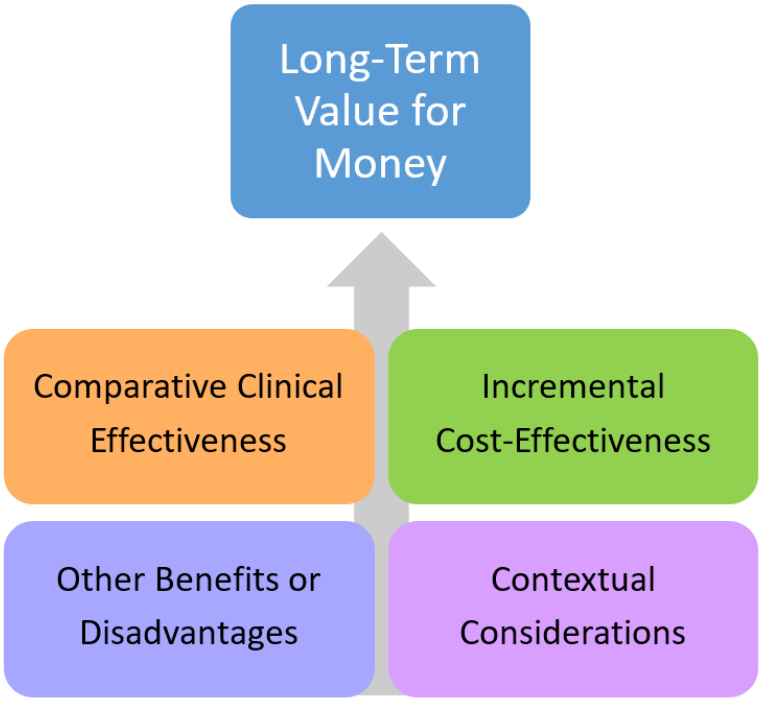
2. Estimated incremental cost-effectiveness is the average incremental cost per patient of one intervention compared to another to achieve a desired "health gain," such as an additional stroke prevented, case of cancer diagnosed, or gain of a year of life. Alternative interventions are compared in terms of cost per unit of effectiveness, and the resulting comparison is presented as a cost-effectiveness ratio. Relative certainty in the cost and outcome estimates continues to be a consideration. As a measure of cost-effectiveness, the [PROGRAM] voting panel follows common academic and health technology assessment standards by using cost per quality-adjusted life year (QALY), with formal voting on "long-term value for money" when the base case incremental cost-effectiveness ratio is between $50,000 per QALY and $175,000 per QALY.

3. Potential other benefits refer to any significant benefits or disadvantages offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. Examples of potential other benefits include better access to treatment centers, mechanisms of treatment delivery that require fewer visits to the clinician's office, treatments that reduce disparities across various patient groups, and new potential mechanisms of action for treating clinical conditions that have demonstrated low rates of response to currently available therapies. Other disadvantages could include increased burden of treatment on patients or their caregivers. For each intervention evaluated, it will be open to discussion whether potential other benefits or disadvantages such as these are important enough to factor into the overall judgment of long-term value for money. There is no quantitative measure for potential other benefits or disadvantages.

4. Contextual considerations include ethical, legal, or other issues (but not cost) that influence the relative priority of illnesses and interventions. Examples of contextual considerations include whether there are currently any existing treatments for the condition, whether the

condition severely affects quality of life or not, and whether there is significant uncertainty about the magnitude of benefit or risk of an intervention over the long term. There is no quantitative measure for contextual considerations.

Figure 9.1. Conceptual Structure of Long-term Value for Money



9.2 Voting Results

1) For patients with hemophilia A without inhibitors to factor VIII, is the evidence adequate to demonstrate that the net health benefit of **emicizumab** (Hemlibra, Genentech) is superior to that provided by prophylaxis with factor VIII?

Yes: 15 votes	No: 0 votes

2) Please vote 1, 2, or 3 on the following potential other benefits and contextual considerations as they relate to **emicizumab**.

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
Uncertainty or overly favorable model assumptions creates significant risk that base-case cost-effectiveness estimates are too optimistic.		Uncertainty or overly unfavorable model assumptions creates significant risk that base-case cost-effectiveness estimates are too pessimistic.
	10 votes	15 votes

Comments: A majority of Councilmembers felt that the economic model assumptions created no significant risk that base-case cost-effectiveness estimates were too optimistic or pessimistic. One Councilmember noted that the disutility of the mode of delivery for emicizumab could lead to problems later in life for the patient, such as avoidance of medical care, and that this may reasonably impact consideration of uncertainty regarding model assumptions.

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
Very similar mechanism of action to that of other active treatments.		New mechanism of action compared to that of other active treatments.
		15 votes

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
Delivery mechanism or relative complexity of regimen likely to lead to much lower real-world adherence and worse outcomes relative to an active comparator than estimated from clinical trials.		Delivery mechanism or relative simplicity of regimen likely to result in much higher real-world adherence and better outcomes relative to an active comparator than estimated from clinical trials.
		15 votes

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
This intervention could reduce or preclude the potential effectiveness of future treatments.		This intervention offers the potential to increase access to future treatment that may be approved over the course of a patient's lifetime.
	15 votes	

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
The intervention offers no special advantages to patients by virtue of presenting an option with a notably different balance or timing of risks and benefits.		The intervention offers special advantages to patients by virtue of presenting an option with a notably different balance or timing of risks and benefits.
3 votes	**9 votes**	3 votes

Comments: Councilmembers who voted 2 or 3 on this question expressed that this referred to the likelihood that even if emicizumab does not prevent development of inhibitors, it likely would delay their development until children are older.

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
This intervention will not differentially benefit a historically disadvantaged or underserved community.		This intervention will differentially benefit a historically disadvantaged or underserved community.
	3 votes	**12 votes**

Comments: The majority of Councilmembers felt that emicizumab will benefit a historically disadvantaged or underserved community. A patient expert noted that the majority of mortality among hemophilia patients in many developed countries in the last 30 years has been caused by the treatment itself. One Councilmember commented on how our current clinical understanding of how to preserve safer blood supply comes at the expense of the historical disadvantages faced by the hemophilia community, and how this should be factored into a judgment of higher value. In addition, another patient expert noted that the ability to sustain an IV prophylactic regimen can be limited (e.g., IV nursing support may not be available) or not accessible; emicizumab, therefore, offers a potential to eliminate such disadvantages. A Councilmember also acknowledged the financial toxicity affecting this community, with the impact of some states not offering Medicaid or some patients unable to afford insurance, and how this contributes to socioeconomic disparities in access to treatment.

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
Small health loss without this treatment as measured by absolute QALY shortfall.		Substantial health loss without this treatment as measured by absolute QALY shortfall.
1 vote	**8 votes**	6 votes

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
Small health loss without this treatment as measured by proportional QALY shortfall.		Substantial health loss without this treatment as measured by proportional QALY shortfall.
3 votes	**10 votes**	2 votes

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
Will not significantly reduce the negative impact of the condition on family and caregivers vs. the comparator.		Will significantly reduce the negative impact of the condition on family and caregivers vs. the comparator.
		15 votes

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
Will not have a significant impact on improving return to work and/or overall productivity vs. the comparator.		Will have a significant impact on improving return to work and/or overall productivity vs. the comparator.
	1 vote	**14 votes**

Comments: The majority of Councilmembers judged that emicizumab will have a significant impact on improving return to work and/or overall productivity when compared to factor VIII prophylaxis. The Council heard from patient experts that in addition to what is shown in RCT data, emicizumab reduces missing work for infusions, allows freedom in the choice of work, allows the ability to travel for work, and to be productive spontaneously.

9.3 Roundtable Discussion and Key Policy Implications

Following its deliberation on the evidence, the New England CEPAC engaged in a moderated discussion with a policy roundtable about how best to apply the evidence on emicizumab and valoctocogene roxaparvovec to policy and practice of hemophilia A care. The policy roundtable members included 2 patient experts, 2 clinical experts, 2 payer representatives, and 3 representatives from pharmaceutical manufacturers. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. The names of the Policy Roundtable participants are shown below, and conflict of interest disclosures for all meeting participants can be found in Appendix G.

Table 9.1 Policy Roundtable Members

Name	Title and Affiliation
Leslie Fish, RPh, PharmD	Vice President of Clinical Pharmacy, IDP Analytics
Richard Ko, MD, MHS, MS	Head of Rare Blood Disorders, US Medical Affairs, Genentech, Inc.
Brian O'Mahony	Chief Executive, Irish Haemophilia Society, Patient Advocate
Steven Pipe, MD	Pediatric Medical Director, Hemophilia and Coagulation Disorders Program, University of Michigan
Margaret Ragni, MD, MPH	Professor of Medicine and Clinical and Translational Medicine, University of Pittsburgh
Mark Skinner, JD	President & CEO, Institute for Policy Advancement Ltd, Patient Advocate
Wing Yen Wong, MD	Group Vice President, Global Medical Affairs, BioMarin Pharmaceutical Inc
John Watkins, PharmD, MPH, BCPS	Formulary Manager, Premera Blue Cross
Todd Williamson, PhD, MSc	Vice President, Data Generation & Observational Studies, Bayer

The roundtable discussion was facilitated by Dr. Steven Pearson, MD, MSc, President of ICER. The main themes and recommendations from the discussion are organized by audience and summarized below.

Manufacturers

Pricing of factor VIII represents a failure of competition and is far too high, even in light of factor VIII's substantial benefits for patients; this pricing structure creates financial toxicity for patients and their families, financial toxicity for health systems, and builds a platform for pricing for potential cures that will only exacerbate these problems.

Factor VIII prices have not come down despite multiple products and the loss of 60% of overall market share to emicizumab. There are several different options for solving this. The US could follow the European model of having the government ask companies to compete for a sole tender

and pick a single or a more limited set of factor VIII products, using a competitive bidding process to keep prices closer to a reasonable alignment with overall patient benefit. Alternatively, in the multi-payer commercial insurance market, PBMs and health plans could seek to use the same approach to seek deeper rebates using narrower formularies, but even large PBMs are likely to lack the market power to restrict access in this way. Perhaps the best way to maintain broad access to multiple agents within a more affordable framework would be for the US to negotiate or set price ceilings for all factor VIII agents based on value assessment. This approach would retain substantial incentives for future innovation, particularly for one-time curative therapies, but would ensure that the prices paid for hemophilia treatment accomplishes more good than the harm that arises from increasing health insurance costs on vulnerable individuals.

In order to facilitate broad access to the current standard for clinically superior care, both in the US and abroad, drug makers should commit to pricing factor VIII so that the cost to achieve trough levels of 3-5% is the same or lower than what it cost in the past to achieve a 1% trough level.

The revenues received by drug companies for factor VIII were already substantial when the accepted minimal standard of care was to seek a 1% trough level. As insurers have moved to cover higher doses to achieve 3-5% troughs it would not be unreasonable to ask drug makers to commit to a shared responsibility for affordability by reducing their prices so that the overall costs of care are held stable while patients and clinicians determine what the optimal trough level should be for each individual patient.

Manufacturers and Researchers should ensure that clinical trials capture a core set of outcomes that are important to patients.

To adequately assess prophylactic therapies for hemophilia, randomized trials need to be performed comparing therapies to each other with outcomes including quality of life and pain. Use of validated measures for quality of life that are sensitive to patient experiences and can be translated into patient utilities would help patients, clinicians, and health technology agencies in assessing therapies. When evaluating gene therapies, the coreHEM outcome set developed with input from multiple stakeholders, including patients and patient groups, is an appropriate starting point; more extensive capture of patient-important outcomes will enhance value assessment.

Trials of gene therapies for hemophilia need to be long enough to assess whether the benefits are durable enough to outweigh the risks, particularly since patients may be unlikely to be able to receive a second gene therapy using the same viral vector.

The request by the FDA for longer-term data on valoctocogene roxaparvovec highlights the fact that the beneficial effects of some gene therapies may not be durable over the intermediate or long term. Given the decline in factor VIII seen over time with valoctocogene roxaparvovec, and the

concerns that gene therapies may have potential harms and may induce immunity to the particular viral vector employed, it is clear that trials must be continued long enough to provide adequate information on the stability and durability of benefits for regulators, patients, clinicians, and payers to judge the relative balance of these benefits to any potential risks. The time horizon for trials will need to be tailored to the specific mechanism of action and early data. For all emerging gene therapies, results should be made public as they become available and should be published and not simply promulgated through press releases showing top line results.

Manufacturers and researchers should study the effects of emicizumab on the development of inhibitors in infancy and early childhood.

Evidence on development of factor VIII inhibitors is critically important. Until this evidence is available, it will be difficult to accurately value emicizumab.

Payers

Payers should cover factor VIII prophylaxis at levels adequate to achieve higher troughs than the 1% level used in the past

All payers should be aware of the widespread consensus among clinical experts and patient organizations that a trough factor VIII level of 3%-5% should be viewed as a minimum target for the vast majority of patients. Clinical experts highlighted that many patients may require higher trough levels depending on their life activities and because individual patients can exhibit different bleeding tendencies at the same factor level. Flexibility is therefore necessary in implementing coverage criteria related to trough levels.

Considering the evidence of equivalent to improved comparative effectiveness, relative convenience, and lower overall cost, emicizumab will be the preferred agent for prophylaxis for many patients. Payers should ensure appropriate access to emicizumab and may wish to share information with clinicians and patients regarding its potential advantages over factor VIII prophylaxis.

Payers may wish to evaluate patterns of care and reach out to talk with clinicians who do not recommend emicizumab for eligible patients. The goal should be to share perspectives on the rationale for the use of emicizumab versus factor VIII.

Payers may wish to require that management of factor VIII be done by or in consultation with a Hemophilia Treatment Center.

Management of hemophilia is both complex and expensive, and HTCs provide consolidated expertise and care through a network of centers of excellence funded by the Federal Government.

Payers should explore innovative approaches to covering high-impact single time therapies such as gene therapies for hemophilia.

Small employers are at risk for severe financial toxicity if one or two of their covered employees/families require a gene therapy, even if that gene therapy may be highly cost-effective over the long term. Payers should therefore consider offering programs that protect plan sponsors (and their employees) by mechanisms such as carved out PMPM coverage plans for cell and gene therapies.

Prior authorization criteria should be based on clinical evidence, specialty society guidelines, and input from clinical experts and patient groups. The process for authorization should be clear and efficient for providers. Options for specific elements of coverage criteria within insurance coverage policy are discussed below.

Clinical Considerations for Emicizumab

Patient Eligibility Criteria

a. **Diagnosis**: Hemophilia A is often diagnosed in infancy based on testing performed at birth if there is a maternal family history or if there is clinical concern raised by bleeding. Repeated testing to confirm eligibility is not necessary.
b. **Patient Population**: Patients eligible for prophylaxis are typically all patients with severe hemophilia A (factor activity level <1%) and some patients with moderate hemophilia A (factor activity level between 1% and 5%) based on clinical phenotype. Patients both with and without inhibitors to factor VIII typically benefit from prophylaxis. For patients who do not meet criteria for severe hemophilia A, payers will likely want to defer to clinicians as to which patients are appropriate for prophylaxis.
c. **Exclusions**: Payers should not exclude patients who have never bled from receiving prophylaxis and should not require a specific number or location of bleeds. A goal of management is to prevent bleeding in patients with severe hemophilia. Additionally, patients who are receiving emicizumab will continue to require access to factor VIII preparations in the event they bleed; emicizumab cannot be used to treat acute bleeds.

Step Therapy

Emicizumab will be preferred by many patients for prophylaxis, and it is a lower cost option from the payer perspective. Payers considering implementing formal step therapy, however, should recognize the heterogeneity of patient experience with factor VIII and its different delivery mechanism. In lieu of formal step therapy, payers may wish to contact clinicians at the time of initiation of prophylaxis if the initial prescription is for factor VIII instead of emicizumab to discuss the clinical situation.

Provider Qualification Restrictions

a. **Payers may wish to require that management of factor VIII be done by or in consultation with a Hemophilia Treatment Center.** Management of hemophilia is expensive, and HTCs provide consolidated expertise and care on a national level. In any case, patients with severe hemophilia A should be managed by, or in consultation with, a hematologist with expertise in clotting disorders.

Patient Advocacy Organizations

Patient groups should fully embrace their power to speak explicitly about the impact of the high prices of treatments for hemophilia A. General statements of concern about "costs" shifts the focus subtly away from prices, which is consistent with the interests of the life science industry. Doing so deflects from the reality that drug makers have the power to set prices in the United States and the result produces affordability concerns for health systems, financial toxicity for patients and families, and barriers to the ability of patients to gain access to optimal clinical care. Hemophilia patient groups should be willing to name the problem and bear witness to the harms that excessive prices cause.

Patient groups should recognize that high prices contribute to financial toxicity for the patients they represent, for other patients with other illnesses, and for all of society.

Patient groups should be fully transparent about the sources and levels of their funding from industry sources.

Patient groups should take pride in making it easy to find information on which drug companies and other health industry sources provide funding, and at what levels. This information should not be relegated to the dense forests of IRS forms or small print in annual reports. Hemophilia patient groups have much to be proud of in their independent voice, but they should match that heritage with a renewed commitment to purposeful transparency on their potential conflicts of interest.

Regulators

Regulators should require manufacturers of expensive therapies such as those for hemophilia A to provide packaging that minimizes wastage.

We heard from payers and clinical experts that real world costs of emicizumab can be substantially higher than the average net price because of vial wastage. We additionally heard that many countries outside the US require packaging that prevents substantial wastage of expensive medications.

All Stakeholders and Policy Makers

It is counterintuitive to pay more for new treatments simply because the existing treatments are overpriced.

As life science companies get closer to bringing a wide range of gene therapies and other potential cures into clinical practice, the celebration that ensues will be shadowed by growing concerns about the affordability of these types of high-impact treatments. Traditional methods for value-based pricing recommendations shift money saved by a cure into the price given to the manufacturer. All stakeholders and policymakers should engage in an open dialogue on the extent to which society wishes to reward innovators more handsomely just because their cure is for a condition that is more expensive to treat. Should a cure arrive for hemophilia A, should the drug maker recoup all the money saved from prevented factor VIII use over decades of time? What proportion of those cost savings should be retained by the health system and used to reduce health insurance costs or pay for other new treatments? This report provided several different scenarios of ways to "share savings" from a potential cure. These options and other ways to address these broader questions should be considered today to prepare for "fair pricing" of the cures of tomorrow.

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This is the second ICER review of emicizumab and first ICER review of valoctocogene roxaparvovec.

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APPENDICES

Appendix A. Search Strategic Results

Table A1. PRISMA 2009 Checklist

		Checklist Items
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.

		Checklist Items
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
RESULTS		
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
DISCUSSION		
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Table A2. Search Strategies for Valoctocogene roxaparvovec, emicizumab and FVIII Inhibitors for Hemophilia A

Table A21. Search Strategy for Interventions: Medline 1996 to Present with Daily Update, and Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations

1	(emicizumab or ace910 or ace 910 or ace-910 or rg6013 or rg 6013 or rg-6013 or emicizumab-kxwh or emicizumab kxwh or hbs910).ti,ab
2	(valoctocogene roxaparvovec or valrox or bmn 270 or bmn270 or bmn-270 or aav5-hfviii or aav5-hfviii-sq or aav5 hfviii or aav5 hfviii sq).ti,ab
3	1 or 2
4	animals.sh.
5	3 not 4
6	limit 5 to english language
7	remove duplicates from 6

Table A22. Search strategy for Interventions: EMBASE SEARCH

1	emicizumab':ti,ab OR 'ace910':ti,ab OR 'ace 910':ti,ab OR 'ace-910':ti,ab OR 'rg6013':ti,ab OR 'rg 6013':ti,ab OR 'rg-6013':ti,ab OR 'emicizumab-kxwh':ti,ab OR 'emicizumab kxwh':ti,ab OR 'hbs910':ti,ab
2	valoctocogene roxaparvovec':ti,ab OR 'valrox':ti,ab OR 'bmn 270':ti,ab OR 'bmn270':ti,ab OR 'bmn-270':ti,ab
3	#1 OR #2
4	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp
5	#3 NOT #4
6	#5 AND [english]/lim

Table A23. Search Strategy for Comparators: Medline 1996 to Present with Daily Update, and Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations

1	h?emophilia a/
2	(hemophilia a or haemophilia a or hemophilia type a or haemophilia type a).ti,ab
3	(classical hemophilia or classical haemophilia or classic hemophilia or classic haemophilia).ti,ab
4	(factor viii adj2 deficienc* or factor 8 adj2 deficienc* or factor viii' adj1 deficienc* or factor 8' adj1 deficienc*).ti,ab
5	1 or 2 or 3 or 4
6	(factor viii product or fviii product or factor 8 product or recombinant factor viii or recombinant fviii or recombinant factor 8 or rfviii or r-fviii or rhfviii or antihemophilic adj1 factor* OR antihaemophilic adj1 factor* OR anti adj1 hemophilic adj1 factor* OR anti adj1 haemophilic adj1 factor*).ti,ab
7	('factor viii' OR 'fviii' OR 'factor 8').ti,ab AND (treatment OR therapy OR treated OR regimen* OR concentrate* OR recombinant OR dose*: OR dosing OR prophylaxis OR prophylactic OR agent* OR medication* OR infusion* OR 'plasma-derived').ti,ab
8	(advate or antihemophilic factor or recombinant or recombin* or rahf-pfm or rahf pfm or octocog alfa).ti,ab
9	(adynovate* or adynovi* or recombinate* or BAX 855 OR BAX-855 OR BAX855 OR SHP660).ti,ab

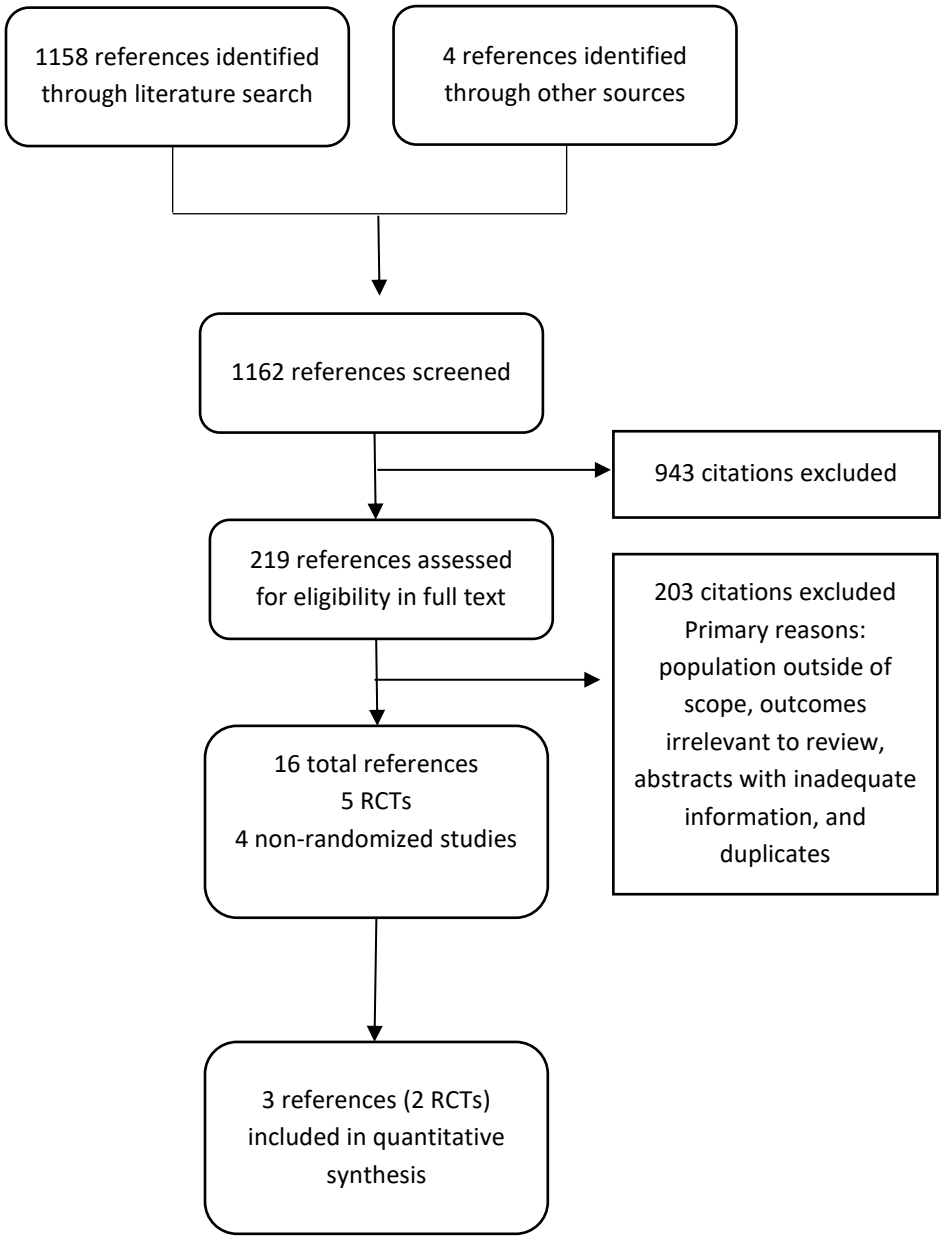
10	(afstyla or rviii-sc or rfviii sc).ti,ab
11	(eloctate or biib031 or rfviiifc or elocta* or elocta or efmoroctocog alfa).ti,ab
12	(humate-p or humate p or haemate-p or haemate p).ti,ab
13	(jivi or bay94-9027 or bay94 9027 or BAY 94 -9027 or BAY 94 9027).ti,ab
14	(kogenate fs or kogenate bayer or bay14-2222 or bay 14 2222 or bay14 2222 or octocog alfa or helixate nexgen).ti,ab
15	(kovaltry or iblias or bay818973 or bay 81 8973 or bay 81-8973).ti,ab
16	(novoeight or n8 or nove eight or nn7008 or nn 7008 or nn-7008 or turoctocog alfa).ti,ab
17	(nuwiq or simoctocog alfa).ti,ab
18	(refacto or xyntha or refacto af).ti,ab
19	(alphanate or fahndi).ti,ab
20	(hemofil m or haemofil m or monarc m).ti,ab
21	(koate or koate dvi or koate-dvi).ti,ab and infusion.ti,ab
22	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23	5 and 22
24	animals.sh
25	23 not 24
26	25 not (case report OR human tissue OR nonhuman OR practice guideline OR questionnaire OR chapter OR conference review OR editorial OR letter OR note OR review OR short survey).pt.
27	26 and (clinical trial or randomized controlled trial or placebo or open label or crossover or cross-over or prospective study or clinical trial or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or multicenter study or randomized controlled trial or (random?ed adj6 (study or trial* or (clinical adj2 trial*)))).ti,ab
28	Limit 27 to English Language
29	Remove duplicates from 28

Table A2.4. Search strategy for Comparators: EMBASE SEARCH

1	'hemophilia a'/exp OR 'haemophilia a'/exp
2	'hemophilia a':ti,ab OR 'haemophilia a':ab,ti OR 'hemophilia type a':ti,ab OR 'haemophilia type a':ti,ab
3	'classical hemophilia':ti,ab OR 'classical haemophilia':ti,ab OR 'classic hemophilia':ti,ab OR 'classic haemophilia':ti,ab
4	(('factor viii' NEAR/4 deficienc*):ti,ab) OR (('factor 8' NEAR/4 deficienc*):ti,ab) OR (('factor viii' NEXT/1 deficienc*):ti,ab) OR (('factor 8' NEXT/1 deficienc*):ti,ab)
5	#1 OR #2 OR #3 OR #4
6	'factor viii product':ti,ab OR 'fviii product':ti,ab OR 'factor 8 product' OR 'recombinant factor viii':ti,ab OR 'recombinant fviii':ti,ab OR 'recombinant factor 8' OR rfviii:ti,ab OR 'r-fviii':ti,ab OR rhfviii:ti,ab OR (antihemophilic NEXT/1 factor*):ti,ab OR (antihaemophilic NEXT/1 factor*):ti,ab OR (anti NEXT/1 hemophilic NEXT/1 factor*):ti,ab OR (anti NEXT/1 haemophilic NEXT/1 factor*):ti,ab

7	'factor viii':ti,ab OR fviii:ti,ab OR 'factor 8':ti,ab AND (treatment:ti,ab OR therapy:ti,ab OR treated:ti,ab OR regimen*:ti,ab OR concentrate*:ti,ab OR recombinant:ti,ab OR dose*:ti,ab OR dosing:ti,ab OR prophylaxis:ti,ab OR prophylactic:ti,ab OR agent*:ti,ab OR medication*:ti,ab OR infusion*:ti,ab OR 'plasma-derived':ti,ab)
8	(advate OR antihemophilic factor OR recombinant OR recombin* OR rahf-pfm OR rahf pfm OR octocog alfa):ti,ab
9	(adynovate* OR adynovi* OR recombinate* OR BAX 855 OR BAX-855 OR BAX855 OR SHP660):ti,ab
10	(afstyla OR rviii-sc OR rfviii sc):ti,ab
11	(eloctate OR biib031 OR rfviiifc OR elocta* OR elocta OR efmoroctocog alfa):ti,ab
12	(humate-p OR humate p OR haemate-p OR haemate p):ti,ab
13	(jivi OR bay94-9027 OR bay94 9027 OR BAY 94 -9027 OR BAY 94 9027):ti,ab
14	(kogenate fs OR kogenate bayer OR bay14-2222 OR bay 14 2222 OR bay14 2222 OR octocog alfa OR helixate nexgen):ti,ab
15	(kovaltry OR iblias OR bay818973 OR bay 81 8973 OR bay 81-8973):ti,ab
16	(novoeight OR n8 OR nove eight OR nn7008 OR nn 7008 OR nn-7008 OR turoctocog alfa):ti,ab
17	(nuwiq OR simoctocog alfa):ti,ab
18	(refacto OR xyntha OR refacto af):ti,ab
19	(alphanate OR fahndi):ti,ab
20	(hemofil m OR haemofil m OR monarc m):ti,ab
21	(koate OR koate dvi OR koate-dvi):ti,ab AND infusion:ti,ab
22	#6 or #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
23	#5 AND #22
24	('animal'/exp or 'nonhuman'/exp or 'animal experiment'/exp) NOT 'human'/exp
25	#23 NOT #24
26	#25 NOT ('case report'/de OR 'human tissue'/de OR 'nonhuman'/de OR 'practice guideline'/de OR 'questionnaire'/de OR 'chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
27	#26 AND ('clinical trial'/de OR 'randomized controlled trial'/de OR 'placebo'/de OR 'open label' OR 'crossover' OR 'cross-over' OR 'prospective study'/de)
28	#27 AND [english]/lim
29	#28 AND [medline]/lim
30	#28 NOT #29

Figure A1. PRISMA flow Chart Showing Results of Literature Search for Valoctocogene roxaparvovec, emicizumab and FVIII Inhibitors for Hemophilia A



Appendix B. Previous Systematic Reviews and Technology Assessments

Reyes A, Révil C, Niggli M, et al. Efficacy of emicizumab prophylaxis versus factor VIII prophylaxis for treatment of hemophilia A without inhibitors: network meta-analysis and sub-group analyses of the intra-patient comparison of the HAVEN 3 trial. Curr Med Res Opin. 2019;35(12):2079-2087.

This systematic literature review and network meta-analysis (NMA) evaluated the efficacy of emicizumab prophylaxis versus factor VIII prophylaxis in patients with hemophilia A without inhibitors. In total, four studies were included in the base case NMA. Of the four studies, three evaluated factor VIII prophylaxis versus no prophylaxis (A-LONG, LEOPOLD, and SPINART), while one evaluated emicizumab prophylaxis versus no prophylaxis (HAVEN 3). Two of the included factor VIII prophylaxis studies evaluated short-acting agents, while one evaluated long-acting factor VIII prophylaxis. The NMA results showed lower treated bleeding rate with emicizumab compared to factor VIII prophylaxis (emicizumab QW [RR 0.36 ;95% CI: 0.13-0.95], emicizumab Q2W [RR 0.31 95% CI: 0.11-0.84. No difference in efficacy was identified between emicizumab QW and Q2W. The authors noted that there was a high degree of heterogeneity among the factor VIII prophylaxis versus no prophylaxis studies (I^2 of 98%).

Appendix C. Ongoing Studies

Title / Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Dates
Emicizumab					
Efficacy, Safety, and Pharmacokinetic Study of Prophylactic Emicizumab Versus No Prophylaxis in Hemophilia A Participants (HAVEN 5) Hoffmann-La Roche NCT03315455	Multi-centered, open-label, Phase III study, with randomized and non-randomized arms Enrollment: 85 Treatment duration: 24 weeks	**Arm 1:** Emicizumab 3 mg/kg subcutaneous injection once weekly for 4 weeks, followed by emicizumab 1.5mg/kg weekly **Arm 2:** Emicizumab 3 mg/kg subcutaneous injection once weekly for 4 weeks, followed by 6 mg/kg every 4 weeks **Arm 3:** No prophylaxis (Control arm) **Arm 4:** Emicizumab 3 mg/kg subcutaneous injection once weekly for 4 weeks, followed by emicizumab 1.5mg/kg weekly	Inclusion • Age ≥12 • Body weight ≥40 kg • ≥5 bleeds in the last 24 weeks • Diagnosis of severe congenital hemophilia A or hemophilia A with FVIII inhibitors Exclusion • Inherited or acquired bleeding disorder other than hemophilia A • Known HIV infection	Model-based annualized bleeding rate for treated bleeds (From baseline to at least 24 weeks) Median calculated annualized bleeding rate for treated bleeds (From baseline to at least 24 weeks) Mean calculated annualized bleeding rate for treated bleeds (From baseline to at least 24 weeks)	March 9, 2022
A Study to Evaluate the Safety, Efficacy,	Multi-centered, open-label, single arm study	Emicizumab 3 mg/kg subcutaneous injection	Inclusion	Model-based annualized bleeding	July 19, 2022

Title / Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Dates
Pharmacokinetics and Pharmacodynamics of Emicizumab in Participants With Mild or Moderate Hemophilia A Without FVIII Inhibitors (HAVEN 6) Hoffmann-La Roche NCT04158648	Enrollment: 70 Treatment Duration: 52 weeks	once weekly for 4 weeks, followed by patient choice of one of the three following regimens: • Emicizumab 1.5mg/kg every week • Emicizumab 3mg/kg every 2 weeks • Emicizumab 6mg/kg every 4 weeks	• Diagnosis of mild (FVIII level between >5% and <40%) or moderate (FVIII level between ≥1% and ≤5%) congenital Hemophilia A without FVIII inhibitors • Body weight ≥3kg • A negative test for inhibitor within 8 weeks prior to enrollment Exclusion • Inherited or acquired bleeding disorder other than hemophilia A • Known HIV infection	rate for treated bleeds (From baseline to at least 52 weeks of emicizumab treatment or 24 weeks after last dose of emicizumab) Median calculated annualized bleeding rate for treated bleeds (From baseline to at least 52 weeks of emicizumab treatment or 24 weeks after last dose of emicizumab) Mean calculated annualized bleeding rate for treated bleeds (From baseline to at least 52 weeks of emicizumab treatment or 24 weeks after last dose of emicizumab)	
Emicizumab PUPs and Nuwiq ITI Study	Non-randomized, parallel assignment, open label, phase III trial	Part 1: Untreated/ minimally treated	**Part A:** Inclusions • Age < 3 years	Annualized bleeding rate (From baseline through duration of	July 2024

Title / Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Dates
Emory University NCT04030052	Enrollment: 60 Treatment Duration: 36 months	severe HA with no inhibitors. • Emicizumab 3 mg/kg subcutaneous injection once weekly for 4 weeks, followed by emicizumab 1.5mg/kg weekly • After receiving emicizumab for 3-6 months, patients then treated with Nuwiq factor VIII 25 units/kg every 2 weeks Part 2: Treated any severity HA with existing inhibitors • Emicizumab 3 mg/kg subcutaneous injection once weekly for 4 weeks, followed by emicizumab 1.5mg/kg weekly • After receiving emicizumab,	• Severe hemophilia A, defined as FVIII level <0.01 IU/ml • No documented FVIII inhibitor since birth Exclusion • Inherited or acquired bleeding disorder other than hemophilia A • Known HIV infection **Part B:** Inclusion • Age < 21 years • Any severity hemophilia A • 2 documented cases of a low or high titer inhibitor Exclusion • Inherited or acquired bleeding disorder other than hemophilia A • Known HIV infection	follow-up [up to 36 months]) Number of target joint bleeds (Time frame: 6 months follow up) Number of target joint bleeds (Time frame: 12 months follow up) Number of adverse events (From baseline through duration of follow-up [up to 36 months])	

Title / Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Dates
		patients then treated with Nuwiq factor VIII 100 units/kg 3 times weekly for 12 months			
Effects of Emicizumab vs. Factor VIII Prophylaxis on Joint and Bone Health in Severe Hemophilia A (EmiMSK) Bloodworks/ Genentech, Inc. NCT04131036	Retrospective/prospective, non-randomized controlled study Enrollment: 40 Treatment Duration: 3 years	**Arm 1:** Emicizumab subcutaneous injections **Arm 2:** Intravenous factor VIII prophylaxis	Inclusion: • Age ≥16 years • Male • Severe hemophilia Exclusions: • Current FVIII inhibitor of > 0.6 BU	Joint health comparison assessed by MSKUS at 3 years compared to baseline	August 2023
The Hemophilia Inhibitor Prevention Trial University of Pittsburgh NCT04303559	Multi-center, phase III, randomized-controlled trial Enrollment: 66 Treatment duration: 48 weeks	**Arm 1:** Emicizumab 3mg/kg subcutaneous injection weekly for 4 weeks. Then, emicizumab 1.5mg/kg weekly **Arm 2:** Eloctate factor VIII 65 IU/kg weekly infusions	Inclusions: • Male • Age >4 months to 4 years • No previous bleed or surgery requiring treatment • No previous factor VIII product Exclusions: • Treatment with clotting factor or	The proportion developing anti-FVIII inhibitors (Timeframe: 48 weeks)	June 2027

Title / Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Dates
			emicizumab previously • Presence of an inhibitor to factor VIII		
A Study to Evaluate the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Subcutaneous Emicizumab in Participants From Birth to 12 Months of Age With Hemophilia A Without Inhibitors (HAVEN 7) Hoffmann-La Roche NCT04431726	Multi-center, phase IIIb, non-randomized, open label trial Enrollment: 50 Treatment Duration: 8 years	Emicizumab 3 mg/kg subcutaneous injection once weekly 4 weeks, then emicizumab 3 mg/kg subcutaneous injection every other week for the next 48 weeks, followed by patient choice of one of the three following regimens for the next 7 years: • Emicizumab 1.5 mg/kg subcutaneous injection every week • Emicizumab 3 mg/kg subcutaneous injection every other week • Emicizumab 6 mg/kg subcutaneous injection every 4 weeks	Inclusions: • Age ≤12 months • Diagnosis of severe hemophilia A • A negative test for FVIII inhibitor and no documented history • Body weight ≥3kg Exclusions: • Inherited or acquired bleeding disorder other than severe hemophilia A • Receipt of any of the following: An investigational drug to treat or reduce the risk of hemophilic bleeds within 5 drug-half-lives of administration	Model-Based, Mean Calculated, and Median Calculated Annualized Bleeding Rate for All Bleeds, Treated Bleeds, Treated Spontaneous Bleeds, and Treated Joint Bleeds [Time Frame: From Baseline to 52 weeks, and during 7-year long-term follow-up period until study completion (up to 8 years)]	December 2029
Valoctocogene Roxaparvovec					

Title / Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Dates
Single-Arm Study To Evaluate The Efficacy and Safety of Valoctocogene Roxaparvovec in Hemophilia A Patients (BMN 270-301) BioMarin Pharmaceutical NCT03370913	Multi-center, open label, single arm, Phase III clinical trial Enrollment: 134 Follow-up: 52 weeks	**Arm 1:** Single administration of valoctocogene roxaparvovec 6E13 vg/kg	Inclusion: • Male • Age ≥18 • Hemophilia A with residual FVIII levels ≤ 1 IU/dL • Factor VIII prophylactic therapy for at least 12 months prior to study entry • No documented history of FVIII inhibitor Exclusions: • Detectable pre-existing antibodies to the AAV5 capsid • Significant liver dysfunction	Change of the median FVIII activity (Timeframe: 52 weeks)	September 2023
Single-Arm Study To Evaluate The Efficacy and Safety of Valoctocogene Roxaparvovec in Hemophilia A Patients at a Dose of 4E13 vg/kg (BMN270-302)	Multi-center, open label, single arm, Phase III clinical trial Enrollment: 40 Follow-up: 52 weeks	**Arm 1:** Single administration of valoctocogene roxaparvovec 4E13 vg/kg	Inclusion: • Male • Age ≥18 • Hemophilia A with residual FVIII levels ≤ 1 IU/dL • Factor VIII prophylactic therapy for at least	Change of the median FVIII activity (Timeframe: 52 weeks)	March 2024

Title / Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Dates
BioMarin Pharmaceutical NCT03392974			12 months prior to study entry • No documented history of FVIII inhibitor Exclusions: • Detectable pre-existing antibodies to the AAV5 capsid • Significant liver dysfunction		
Gene Therapy Study in Severe Hemophilia A Patients With Antibodies Against AAV5 (270-203) BioMarin Pharmaceutical NCT03520712	Multi-center, open label, single arm, Phase I/II clinical trial Enrollment: 10	Arm 1: Single administration of valoctocogene roxaparvovec 6E13 vg/kg	Inclusion: • Male • Age ≥18 • Hemophilia A with residual FVIII levels ≤ 1 IU/dL • Detectable pre-existing antibodies to the AAV5 capsid • Factor VIII prophylactic therapy for at least 12 months prior to study entry • No documented history of FVIII inhibitor Exclusion:	Percentage of participants with treatment-related adverse events for 5 years following infusion	June 2025

Title / Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Dates
			• Significant liver dysfunction		
Study to Evaluate the Efficacy and Safety of Valoctocogene Roxaparvovec, With Prophylactic Steroids in Hemophilia A (GENEr8-3) BioMarin Pharmaceutical NCT04323098	Multi-center, open label, single arm, Phase IIIb clinical trial Enrollment: 20	**Arm 1:** Single administration of valoctocogene roxaparvovec 6E13 vg/kg with prophylactic corticosteroids	Inclusion: • Male • Age ≥18 • Hemophilia A with residual FVIII levels ≤ 1 IU/dL • Factor VIII prophylactic therapy for at least 12 months prior to study entry • No documented history of FVIII inhibitor Exclusions: • Detectable pre-existing antibodies to the AAV5 capsid • Significant liver dysfunction	Change of the median FVIII activity (Timeframe: 52 weeks)	December 2025

Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies)

Appendix D. Comparative Clinical Effectiveness Supplemental Information

We performed screening at both the abstract and full-text level. A single investigator screened all abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. One investigator reviewed full papers and provided justification for exclusion of each excluded study.

We also included FDA documents related to valoctocogene roxaparvovec and emicizumab. These included the manufacturer's submission to the agency, internal FDA review documents, and the transcript of Advisory Committee deliberations and discussions. All literature that did not undergo a formal peer review process is described separately.

We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories "good," "fair," or "poor" (see Appendix Table F2) [93] Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

Good: *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.*

Fair: *Studies were graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.*

Poor: *Studies were graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.*

Note that case series are not considered under this rating system – because of the lack of comparator, these are generally considered to be of poor quality.

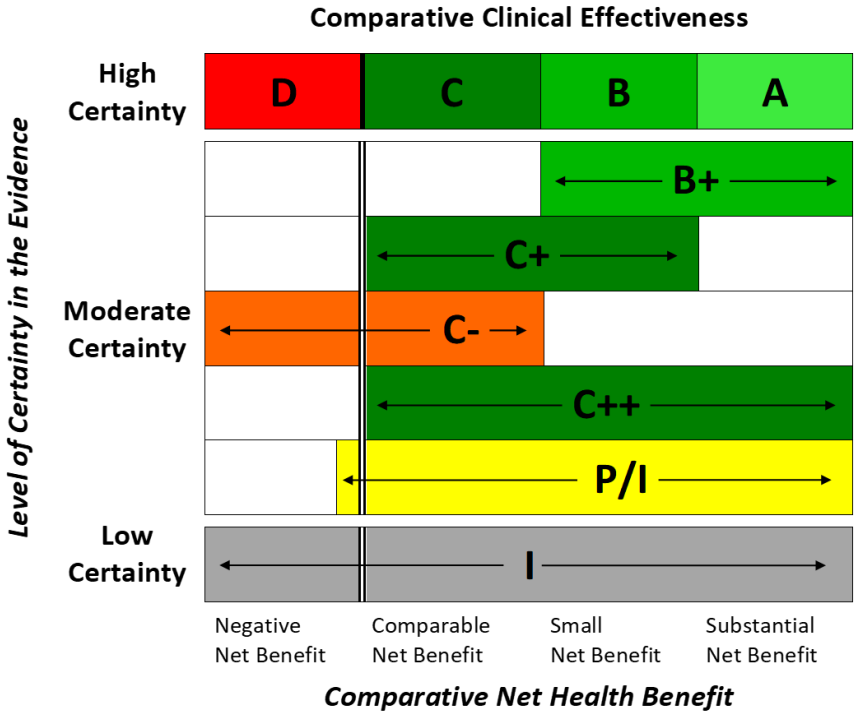
ICER Evidence Rating

We used the ICER Evidence Rating Matrix (see Figure D1) to evaluate the evidence for a variety of outcomes. The evidence rating reflects a joint judgment of two critical components:

6. The magnitude of the difference between a therapeutic agent and its comparator in "net health benefit" – the balance between clinical benefits and risks and/or adverse effects; and

7. The level of certainty in the best point estimate of net health benefit.[64,65]

Figure D.1. ICER Evidence Rating Matrix



***A = "Superior"** - High certainty of a substantial (moderate-large) net health benefit*
***B = "Incremental"** - High certainty of a small net health benefit*
***C = "Comparable"**- High certainty of a comparable net health benefit*
***D= "Negative"**- High certainty of an inferior net health benefit*
***B+= "Incremental or Better" –** Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
***C+ = "Comparable or Incremental" -** Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit*
***C- = "Comparable or Inferior" –** Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit*
***C++ = "Comparable or Better" -** Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
***P/I = "Promising but Inconclusive"** - Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit*
***I = "Insufficient" –** Any situation in which the level of certainty in the evidence is low*

Abstraction Tables

Table D1. Valoctocogene Roxaparvovec and Emicizumab

Author & Year of Publication (Trial) Quality Rating	Study Design and Duration of Follow-up	Inclusion and Exclusion Criteria	Interventions (n) & Dosing Schedule	Patient Characteristics	Outcomes	Harms
Emicizumab						
Mahlangu NEJM 2018[21] (HAVEN 3) *Good quality*	Phase 3, open-label, randomized trial Follow up: At least 24 weeks 39 sites in 13 countries (United States, Australia, Costa Rica, France, Germany, Ireland, Italy, Japan, Japan, Korea, Poland, South Africa, Spain, Taiwan, United Kingdom)	**Inclusion** -12 years of age or older - severe hemophilia A without inhibitors to factor VIII -Previously receiving episodic or prophylactic treatment with FVIII therapy **Exclusion** -Inherited or acquired bleeding disorder other than hemophilia A -Treatment within the last 12 months for, or current signs of, thromboembolic disease	**Patients on prior episodic FVIII treatment were randomized to:** 1) Emicizumab SC 1.5mg/kg weekly (n =36) 2) Emicizumab SC 3mg/kg every other weekly (n =35) 3) No prophylaxis (n=18) **All patients previously on adequate prophylactic FVIII were assigned to:** 4) Emicizumab SC 1.5mg/kg weekly (n =63) All patients were given loading doses of 3 mg/kg per week for 4 weeks Patients could receive FVIII (investigation-	**Median Age (range)** (1) 37 (19-77) (2) 41 (20-65) (3) 40 (16-57) (4) 36 (13-68) **Male, %** 100% male in all groups **Participants without FVIII inhibitors, %** 100% in all groups **Severe Hemophilia, %** 100% in all group (based on inclusion criteria) **Presence of target Joint, n (%)** (1) 34 (94) (2) 27 (77) (3) 15 (83)	**Randomized comparison in patients on prior episodic treatment:** **Model based ABR (95% CI); p-value vs. group 3 at week 24** *Treated bleeds* (1) 1.5 (0.9-2.5) ; P,0.001 (2) 1.3 (0.8-2.3) ; P<0.001 (3) 38.2 (22.9-63.8) *All (treated & untreated)* (1) 2.5 (1.6-3.9) ; P<0.001 (2) 2.6 (1.6-4.3) ; P<0.001 (3) 47.6 (28.5-79.6) *Treated joint bleeds* (1) 1.1 (0.6-1.9) ; P<0.001 (2) 0.9 (0.4-1.7) ; -P<0.001 (3) 26.5 (14.7-47.8) *Treated target joint bleeds* (1) 0.6 (0.3-1.4) ; P<0.001 (2) 0.7 (0.3-1.6) ; P<0.001 (3) 13.0 (5.2-32.3) **Quality of life, difference in Haem-A-QOL vs. control (95% CI)** (1) 12.5 (-2.0-27.0) (2) 16.0 (1.2-30.8) (3) control	**All patients** **Mortality, n(%)** (1) 0 (0%) (2) 0 (0%) (3) 0 (0%) (4) 0 (0%) **Serious AEs, N** (1) 1 (2) 3 (3) 0 (4) 0 **Thrombosis, n(%)** (1) NR (2) NR (3) NR (4) NR **Injection-Site reaction, n(%)** (1) 9(25%) (2) 7(20%) (3) 2(12%) (4) 20(32%)

Author & Year of Publication (Trial) Quality Rating	Study Design and Duration of Follow-up	Inclusion and Exclusion Criteria	Interventions (n) & Dosing Schedule	Patient Characteristics	Outcomes	Harms
			determined doses) for breakthrough bleeding	(4) 26 (41) **<9 bleeds in 24 wks prior to trial, n (%)** (1) 9 (25) (2) 5 (14) (3) 4 (22) (3) 53 (84)		
Mahlangu NEJM 2018[21] (HAVEN 3 – intra-individual comparison) *Good quality* (Additional References: Oldenburg 2019[22])	Phase 3, open-label, randomized trial (*See Mahlangu NEJM 2018 above)* Design was open label for the intra-individual comparison Majority of patients that participated in open label emicizumab participated in prior prospective non-interventional study (NIS) for at least at least 24 weeks	*See Mahlangu NEJM 2018 above*	**Patients previously on adequate prophylactic FVIII who had participated in a NIS** 1) Factor VIII prophylaxis during NIS (n=48) 2) Emicizumab SC 1.5mg/kg weekly during HAVEN 3 (n =48)	**Patients specifically in NIS not reported** *(See Mahlangu NEJM 2018 above for all patients)*	**<u>Intra-individual comparison in patients on prior adequate prophylactic FVIII</u>** **<u>Randomized comparison in patients on prior episodic treatment:</u>** **Model based ABR (95% CI); p-value vs. group 3** *Treated bleeds* (1) 1.6 (1.1-2.4) ; P<0.001 (2) 4.8 (3.2-7.1) *All (treated & untreated)* (1) 3.3 (2.2-4.8); p<0.0002 (2) 8.9 (5.7-13.9) *Treated joint bleeds* (1) 1.2 (0.7-2.0) (2) NA *Treated target joint bleeds* (1) 0.6 (0.3-1.5)	*See Mahlangu NEJM 2018 above for all patients*

Author & Year of Publication (Trial) Quality Rating	Study Design and Duration of Follow-up	Inclusion and Exclusion Criteria	Interventions (n) & Dosing Schedule	Patient Characteristics	Outcomes	Harms
					(2) NA **Quality of life, difference in Haem-A-QOL vs. control (95% CI)** (1) NR (2) NR	
Pipe Lancet 2019[23] (HAVEN 4) (Additional references: Skinner 2019[26])	Phase 3, open-label, multicenter, 2-stage trial (run-in phase* to assess pharmacokinetics & expansion phase to assess efficacy) Follow up: At least 24 weeks 17 sites in 6 countries (Australia, Belgium, Japan, Poland, Spain, and the USA) *Run-in phase not abstracted	**Inclusion** -12 years of age or older -Severe hemophilia A or hemophilia with inhibitors undergoing treatments with FVIII concentrates or bypassing agents -Patients on episodic treatment were required to have ≥5 bleeds in the 24 weeks before study entry **Exclusion** -Patients who are at high risk for thrombotic microangiopathy -previous (within 12 months) or current thrombotic disease	**Patients on prior episodic FVIII treatment were randomized to:** 1) Emicizumab SC 6mg/kg weekly (n =41) Patients were given loading doses of 3 mg/kg per week for 4 weeks Patients could receive FVIII (investigation-determined doses) for breakthrough bleeding	**Median Age (range)** (1) 39 (14-68) **Male, n (%)** (1) 41 (100) **Participants without FVIII inhibitors, n (%)** (1) 36 (88) **Severe Hemophilia, %** (1) 40 (98) **Presence of target Joint, n (%)** (1) 25 (61) **Median number of bleeds in the 24 wks prior to trial (range)** (1) 5 (0-90)	**Patients on prior episodic FVIII treatment:** **Model based ABR (95% CI)** *Treated bleeds* (1) 2.4 (1.4-4.3) *All (treated & untreated)* (1) 4.5 (3.1-6.6) *Treated joint bleeds* (1) 1.7 (0.8-3.7) *Treated target joint bleeds* (1) 1.0 (0.3-3.3) **Pooled Quality of life Haem-A-QoL changes from BL in participants ≥18, mean (SD)** Week 25 -15.1 (21.9) Week 49 -17.4 (20.6) Week 61 -18.4 (23.2) Week 73	**Serious AE** (1) 1(2%) **AE leading to withdrawal from treatment** (1) 0(0%) **AE leading to dose modification or interruption** (1) 0 (0%) **Treatment related AE** (1) 12(29%) **Treatment related local injection-site reaction** (1) 9(22%) **Grade ≥3** (1) 1(2%) **Grade 2** (1) 14(34%)

Author & Year of Publication (Trial) Quality Rating	Study Design and Duration of Follow-up	Inclusion and Exclusion Criteria	Interventions (n) & Dosing Schedule	Patient Characteristics	Outcomes	Harms
					NE	**Grade 1** (1) 15(37%) **Nasopharyngitis** (1) 11(27%)
Callaghan 2019[25] (abstract)	Pooled data on long-term efficacy and safety of emicizumab in phase III studies Follow-up: 98 weeks	**Inclusion** -Pediatric and adolescent/adult PwHA -With or without inhibitors -All patients assigned to emicizumab **Exclusion** NR	1)Haven 1 (n=113) 2) Haven 2 (n=88) 3) Haven 3 (n=151) 4) Haven 4 (n=48) *only reporting data from Haven 3 and 4	*See Mahlangu NEMJ 2018 and Pipe Lancet 2019 above*	**Pooled Mean Annualized Bleed Rate in Patients Taking Emicizumab in HAVEN 3 and 4 (95% CI)** <u>1-24 weeks</u> 3) 1.8 (0.2-7.0) 4) 2.1 (0.3-7.4) <u>25-48 weeks</u> 3) 0.9-0.0-5.5) 4) 1.5 (0.1-6.4) <u>49-72 weeks</u> 3) 0.9 (0.0-5.5) 4) NE <u>73-96 weeks</u> 3) 0.2 (0.0-4.1) 4) NE	*See Mahlangu NEMJ 2018 and Pipe Lancet 2019 above*
Shima Hemophilia 2019[24] (HOHOEMI)	Multicenter, open-label, non-randomized, efficacy, safety, and pharmacokinetics Follow-up: at least 24 weeks	**Inclusion** -<12 years old, weighing over 3kg -Severe congenital hemophilia A without FVIII inhibitors -Tested negative for inhibitors within 8	1)maintenance dose of 3mg/kg emicizumab Q2W (n=6) 2)maintenance dose of 6mg/kg emicizumab Q4W (n=7)	**Age (y), median (range)** (1) 6.6 (1.5-10.7) (2) 4.1 (0.3-8.1) **Weight (kg), median (range)** (1) 19.5 (10.9-35.6) (2) 15.7 (6.6-25.6)	**Model based ABR (95% CI)** *Treated bleeds* (1) 1.3 (0.6-2.9) (2)0.7 (0.2-2.6) *All (treated & untreated)* (1) 14.1 (7.6-26.2) (2) 21.8 (9.2-51.8) *Treated joint bleeds*	No thromboembolic events, TMA, or systematic hypersensitivity reactions were observed. Only one event of injection site reaction was

Author & Year of Publication (Trial) Quality Rating	Study Design and Duration of Follow-up	Inclusion and Exclusion Criteria	Interventions (n) & Dosing Schedule	Patient Characteristics	Outcomes	Harms
	4 centers in Japan	weeks prior to enrollment -Documentation of bleeding episodes and treatment with coagulation factors was required in 12 weeks prior to enrollment for patients <2 years old and 24 weeks prior for patients ≥2 years old **Exclusion** -Complication of a bleeding disorder other than hemophilia a -thromboembolic diseases within the past 12 months -High risk of thrombotic microangiopathy (TMA) -or familial history of TMA	Each cohort received a loading dose of 3 mg/kg QW for the first 4 weeks Patients who had received FVIII prophylaxis prior to enrollment were permitted to continue FVIII prophylaxis until receiving the second loading dose of emicizumab. FVIII products were administered for breakthrough bleeding, as necessary.	**Patients treated with FVIII prophylaxis prior to enrollment, n(%)** (1) 6(100%) (2) 6(85.7) **Previously untreated patients (PUPs), n(%)** (1) 0(0%) (2) 1(14.3) **Patients with target joints, n(%)** (1) 1 (16.7%) (2) 0 (0%)	(1) 0.9 (0.3-2.3) (2) NE *Treated target joint bleeds* (1) NE (2) NE	considered to be related to treatment in the Q2W cohort and was resolved without any treatment **Total patients with ≥AE, n(%)** (1) 6 (100%) (2) 7 (100%) **Nasopharyngitis n(%)** (1) 2 (33.3%) (2) 3(42.9) **Contusion, n(%)** (1) 4 (66.7) (2) 6 (85.7)
Valoctocogene Roxaparvovec						
Rangarajan 2017[13] **Pasi 2020**[10] Phase I/II	Phase I/II, multicenter, dose escalation, safety, and efficacy study	**Inclusion** -Adults with hemophilia a	1) Cohort 1 Low dose 6x10^12 vg/kg (n=1)**	**Median age (range)** (1) 25 (NA) (2) 43 (NA)	**Cohort 3 Results** **FVIII Activity Level** CS / OS	**Any AE** (1) 100% (2) 100% (3) 100%

<table>
<tr><th>Author & Year of Publication (Trial) Quality Rating</th><th>Study Design and Duration of Follow-up</th><th>Inclusion and Exclusion Criteria</th><th>Interventions (n) & Dosing Schedule</th><th>Patient Characteristics</th><th>Outcomes</th><th>Harms</th></tr>
<tr>
<td>Additional Publications: BioMarin PowerPoint[14], BioMarin R&D[15], BioMarin WFH Conference presentation[18,19]</td>
<td><u>Follow-Up:</u> up to 3 years
5 sites in the united kingdom</td>
<td>-No history of FVIII inhibitor development
-At least 50 days of previous exposure to FVIII concentrate
Patients on on-demand therapy
-at least 12 bleeding events (defined as a bleed event requiring FVIII replacement treatment) in previous 12 months were required

Exclusion
-HIV
-Any evidence of active infection or immunosuppressive disorder
-Evidence of any bleeding disorder not related to hemophilia
-Significant liver dysfunction
-Major surgery planned in the 16-week period following infusion</td>
<td>2) Cohort 2 Intermediate dose 2x10^13 vg/kg (n=1)**
3) Cohort 3 high dose 6x10^13 vg/kg (n=7)
4) Cohort 4 4x10^13 vg/kg (n=5)*

**Data for cohort 1 and 2 not reported

***The study protocol required the initiation of a therapeutic course of prophylactic prednisolone at a dose of 40 mg per day, tapering from week 3 to week 17 or longer.</td>
<td>(3) 30 (23-42)
(4) 31.3 (22-45)

Male, N(%)
100% male in all groups

Type of replacement therapy
(1) Prophylactic (100%)
(2) Prophylactic (100%)
(3) Prophylactic (85%), on-demand (15%)
(4) Prophylactic (100%)

ABR in year before enrollment (range)
(1) 2 (NA)
(2) 3 (NA)
(3) 16 (0-40)*
(4) 12 (0-41)

* value was not available for one participant</td>
<td>
<table>
<tr><th></th><th>Mean (median)</th><th>Mean (median)</th></tr>
<tr><td colspan="3">Cohort 3</td></tr>
<tr><td>Y1</td><td>64 (60)</td><td>104 (89)</td></tr>
<tr><td>Y2</td><td>36 (26)</td><td>59 (46)</td></tr>
<tr><td>Y3</td><td>33 (20)</td><td>52 (30)</td></tr>
<tr><td>Y4</td><td>24.2(16.4)</td><td>35.4(23.4)</td></tr>
</table>
Annualized FVIII Usage
<table>
<tr><th></th><th>Mean</th><th>% Reduced</th></tr>
<tr><td colspan="3">Cohort 3</td></tr>
<tr><td>BL</td><td>136.7</td><td rowspan="5">96%</td></tr>
<tr><td>Y1</td><td>2.1</td></tr>
<tr><td>Y2</td><td>8.8</td></tr>
<tr><td>Y3</td><td>5.5</td></tr>
<tr><td>Y4</td><td>4.6</td></tr>
</table>
Annualized Bleeding Rate
<table>
<tr><th></th><th>Mean</th><th>Median</th><th>N w/0 Bleed</th></tr>
<tr><td colspan="4">Cohort 3</td></tr>
<tr><td>BL</td><td>16.3</td><td>16.5</td><td>17</td></tr>
<tr><td>Y1</td><td>0.9</td><td>0</td><td>71</td></tr>
<tr><td>Y2</td><td>0.2</td><td>0</td><td>86</td></tr>
<tr><td>Y3</td><td>0.7</td><td>0</td><td>86</td></tr>
<tr><td>Y4</td><td>1.3</td><td>0</td><td>86</td></tr>
<tr><td>%</td><td colspan="3">95%</td></tr>
</table>
Mean Total Score in hrQoL
<table>
<tr><th></th><th>N</th><th>Cohort 3</th></tr>
<tr><td>Week 0</td><td>7</td><td>71.8</td></tr>
<tr><td>Week 52</td><td>7</td><td>81.4</td></tr>
</table>
</td>
<td>(4) 100%
Treatment Related AE
(1)100%
(2) 0%
(3) 85.7%
(4) 100%
Any Serious AE
(1) 0%
(2) 0%
(3) 28.6%
(4) 16.7%
AE Leading to D/C
No Participants discontinued due to treatment
AST
(1) 100%
(2) 0%
(3) 85.7%
(4) 66.7%
Treated ALT Elevation
(1) 0%
(2) 0%
(3) 85.7%
(4) 66.7%
Nasopharyngitis
(1) 100%
(2) 100%
(3) 71.4%
(4) 50.0%</td>
</tr>
</table>

<table>
<tr><th>Author & Year of Publication (Trial) Quality Rating</th><th>Study Design and Duration of Follow-up</th><th>Inclusion and Exclusion Criteria</th><th>Interventions (n) & Dosing Schedule</th><th>Patient Characteristics</th><th>Outcomes</th><th>Harms</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>
<table>
<tr><td>Week 104</td><td>5</td><td>86.2</td></tr>
<tr><td>Week 156</td><td>6</td><td>87.0</td></tr>
<tr><td>Week 208</td><td>5</td><td>88.0</td></tr>
</table>
</td><td></td></tr>
<tr><td>Rangarajan 2017[13]
Pasi 2020[10]

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Additional Publications: BioMarin PowerPoint[14], BioMarin R&D[15], BioMarin WFH conference presentation[18,19]</td><td>See Rangarajan 2017 above</td><td>See Rangarajan 2017 above</td><td>1) Cohort 1 Low dose 6x10^12 vg/kg (n=1)**
2) Cohort 2 Intermediate dose 2x10^13 vg/kg (n=1)**
3) Cohort 3 high dose 6x10^13 vg/kg (n=7)
4) Cohort 4 4x10^13 vg/kg (n=5)*

*Only 2 years of data is available for patients in cohort 4</td><td>See Rangarajan 2017 above</td><td><u>Cohort 4 Results</u>
FVIII Activity Level
<table>
<tr><th></th><th>CS Mean (median)</th><th>OS Mean (Median)</th></tr>
<tr><td>Cohort 4</td><td></td><td></td></tr>
<tr><td>Y1</td><td>21.0 (23)</td><td>31 (32)</td></tr>
<tr><td>Y2</td><td>15 (13)</td><td>23 (24)</td></tr>
<tr><td>Y3</td><td>9.9 (7.9)</td><td>14.9(12.3)</td></tr>
<tr><td>Y4</td><td>N/A</td><td>N/A</td></tr>
</table>
Annualized FVIII Usage
<table>
<tr><th></th><th>Mean (IU/dL)</th><th>% Reduced</th></tr>
<tr><td>Cohort 4</td><td></td><td></td></tr>
<tr><td>BL</td><td>146.5</td><td rowspan="4">96%</td></tr>
<tr><td>Y1</td><td>2</td></tr>
<tr><td>Y2</td><td>6.8</td></tr>
<tr><td>Y3</td><td>8.4</td></tr>
<tr><td>Y4</td><td>N/A</td><td>N/A</td></tr>
</table>
Annualized Bleeding Rate
<table>
<tr><th></th><th>Mean</th><th>Median</th><th>N w/ Bleed</th></tr>
<tr><td>Cohort 4</td><td></td><td></td><td></td></tr>
<tr><td>BL</td><td>12.2</td><td>8</td><td>17</td></tr>
<tr><td>Y1</td><td>0.9</td><td>0</td><td>83</td></tr>
<tr><td>Y2</td><td>1.2</td><td>0</td><td>67</td></tr>
<tr><td>Y3</td><td>0.5</td><td>0</td><td>67</td></tr>
<tr><td>Y4</td><td>N/A</td><td>N/A</td><td>N/A</td></tr>
</table>
</td><td>See Rangarajan 2017 above</td></tr>
</table>

Author & Year of Publication (Trial) Quality Rating	Study Design and Duration of Follow-up	Inclusion and Exclusion Criteria	Interventions (n) & Dosing Schedule	Patient Characteristics	Outcomes	Harms
					% 93% **Mean Total Score in HrQoL** **N** / **Cohort 4** **Week 0** 6 80.9 **Week 52** 4 82.4 **Week 104** 6 77.7 **Week 156** 6 83.0 **Week 208** N/A N/A	
BioMarin Press Release[16] **BioMarin Powerpoint**[14] **Phase III GENEr8-1**	Phase III, open-label single arm study, Follow-up 26 weeks	**Inclusion** -Males >18 years old =hemophilia A diagnosis and residual FVIII levels ≤ 1 IU/dL -Must be on prophylactic FVIII therapy for at least 12 months prior to study entry -No history of FVIIII inhibitor -HIV positive patients may be enrolled **Exclusion** -Detectable pre-existing antibodies to the AAV5 capsid -Any evidence of active infection or immunosuppressive disorder, except HIV	1) valoctocogene roxaparvovec 6E13 vg/kg (n=20)	*Not Yet Reported*	**Annualized Bleeding Rate (n=16)** Pre-Infusion Median: 0.9 Mean: 9.9 Post-Infusion Median: 0 Mean: 1.5 % Reduction: 85% **Annualized FVIII Usage (n=16)** Pre-infusion Median: 132.7 Mean: 146.1 Post-Infusion Median: 1.2 Mean: 6.6 % Reduction: 95% **FVIII Activity at 23-26 weeks (N= 16)** Max: 84.0 Mean: 36.3 Median: 33.1 Min: <1	No patients withdrew from the study **Serious Adverse Events** (1) 3(13.6) **ALT Elevation** (1) 17(77.3) **Nausea** (1) 11 (50) **Headache** (1) 10 (45.5) **Fatigue** (1) 9 (40.9) **AST** (1) 8 (36.4)

Author & Year of Publication (Trial) Quality Rating	Study Design and Duration of Follow-up	Inclusion and Exclusion Criteria	Interventions (n) & Dosing Schedule	Patient Characteristics	Outcomes	Harms
		-Active malignancy, except non-melanoma skin cancer				
BioMarin Press Release[16] **Phase III GENEr8-2**	Phase III, open-label single arm study, Follow-up: unclear	*See above GENEr8-1 study*	1) valoctocogene roxaparvovec 4E13 vg/kg (n=20) *dose seems to have been discontinued	*Not yet Reported*	*Not yet Reported*	*Not yet Reported*

AE: adverse events, AST: aspartate transaminase, ALT: alanine aminotransferase, BL: baseline, CI: confidence interval, d/c: discontinuation, FVIII: factor 8, HrQol: hemophilia related quality of life, N/A: not applicable, NE: not estimable, Q2W: every 2 weeks, Q4W: every 4 weeks, Y: year, %: percent reduction, CS: chromogenic substrate assay, OS:one-stage assay

Table D2. FVIII Studies

Author & Year of Publication (Trial) Quality Rating	Study Design and Duration of Follow-up	Inclusion and Exclusion Criteria	Interventions (n) & Dosing Schedule	Patient Characteristics	Outcomes	Harms
Factor VIII						
Manco-Johnson 2013[28] **Manco-Johnson 2013** **Manco-Johnson 2017[27]** ***SPINART*** *Good quality*	Phase IIIb/IV randomized, controlled, parallel-group, open-label study Follow-up: 3 years	**Inclusion** -Males -Age 12 to 50 (aged 18-50 in Bulgaria and Romania) -Severe hemophilia A -No FVIII inhibitor status or history -6 to 24 documented bleeding events or treatments in past 6 months **Exclusions:** -Bleeding disorders other than Hemophilia A -Thrombocytopenia (defined as platelet count <100,000mm^{-3}) -Abnormal renal function -Active hepatic disease -Use of immunomodulating agents in last 3 months	1) Factor VIII prophylaxis 25 IU/kg 3 times weekly. Dose may be increased by 5 IU/kg at the end of year 1 and end of year 2 toa maximum dose of 30 or 35 IU kg 2) Factor VIII on-demand dosing per investigator's clinical recommendation	**Median Age (Range)** 1) 29.0 (15-50) 2) 29.0 (17-48) **Factor VIII Level <1%, n (%)** 1) 39 (92.9%) 2) 42 (100%) **Presence of Target Joints, yes n (%)** 1) 28 (66.7%) 2) 31 (73.8%) **Median Bleeding Episodes in Last 6 Months (Range)** 1) 9.0 (2-23) 2) 12.0 (6-24) **Median Bleeding Episodes in Last 12 Months (Range)** 1) 17.0 (6-42) 2) 19.5 (8-47)	**ABR Treated Bleeds (SD)** 70 Weeks 1) 2.2 (5.1) 2) 36.9 (23.8) 156 Weeks 1) 2.5 (4.7) 2) 37.2 (19.9) **ABR Treated Joint Bleeds (SD)** 70 Weeks 1) 1.9 (4.7) 2) 29.2 (20.6) 156 Weeks 1) 1.9 (4.1) 2) 28.7 (18.8) **Quality of life Haem-A-QoL changes from BL (95% CI)** 1) +3.98 points (-1.14 to +9.10; median: 4.40) 2) -6.00 points (-11.62 to -0.38; median: 0.27) Treatment Difference): 9.98 points (3.42 to 16.54, p=0.0034) favoring prophylaxis	**Any AE** 1) 59.5% 2) 88.1% **Serious AE** 1) 21.4% 2) 28.6% **Treatment-Related AE** 1) 0% 2) 0%

FVIII: factor 8, IU/kg: international units per kilogram, n: number, SD: standard deviation, ABR: annualized bleed rate, CI: confidence interval, QOL: quality of life, AE: adverse event

Supplemental NMA Information

Table D3. NMA Feasibility Assessment

Trial	Study design	Study Duration	Interventions	Number of patients	Median age, years	Range age, years	Primary outcome assessed based on definition	NMA decision Include or Exclude
HAVEN 3[21] (Emicizumab)	Open label, randomized, multicenter trial	At least 6 months	Emicizumab 1.5 mg QW	36	36.5	19-77	Treated bleed	Include
			Emicizumab 3mg Q2W	35	41	20-65		
			On-demand FVIII	18	40	16-57		
SPINART[27,28] (Kogenate) [Manco-Johnson 2013 and Manco-Johnson 2017]	Open label, randomized, multicenter trial	3 years	FVIII Prophylaxis	42	29	17-48	Treated bleed	Include
			On-demand FVIII	42	29	17-50		
LEOPOLD 2 (Kovaltry) [Kavakli 2015][67]	Open-label, randomized crossover, multicenter trial	6 months each phase	FVIII Prophylaxis 2/wk	28	27	14-54	All bleeds	Exclude (see Table D4 below)
			FVIII Prophylaxis 3/wk	31	28	14-59		
			On-demand FVIII	21	30	14-53		
A-LONG (EloctateV)[68] [Mahlangu 2014]	Open-label, partially randomized, multicenter trial	Median: 28 weeks	Individualized Prophylaxis	118	29	16-65	Treated bleeds	Exclude (see Table D4 below)
			Weekly Prophylaxis	24	31.5	18-59		
			On-demand FVIII	23	34	13-62		
ESPRIT[69] [Gringerii 2011]	Open-label, randomized, pragmatic multicenter trial	10 years	FVIII Prophylaxis 3/wk	21	4.1	1– 7	Treated bleeds	Exclude (see Table D4 below)

Table D4. Randomized trials of factor VIII prophylaxis excluded from NMA

Trials	Reasons for not including in NMA
LEOPOLD 2 (Kovaltry)[67] [Kavakli 2014]	Outcome definition: This study defined bleeding event as spontaneous bleeds, trauma-related bleeds, untreated bleeds, and unspecified events for which treatment was administered. As such a determination was made that the study reported 'all bleeding events' (and not treated bleeds that was the main outcome for the NMA). To further support this, the means of the annual bleeding rates in what would be the common comparator arms in the NMA (no prophylaxis arms) were vastly different from treated bleeds in HAVEN 3 (LEOPOLD 2: 57.5 versus HAVEN 3: 38.3).
A-LONG (EloctateV)[68] [Mahlangu 2014]	Study design: A-LONG was a partially randomized trial. The non-randomized arm of the study was for patients continuing factor VIII prophylaxis (EloctateV) at the FDA recommended dose (25-56 IU/KG at a dosing interval of 3-5 days). The randomized part of the study included no prophylaxis arm and weekly factor VIII prophylaxis, which is less frequent than the FDA recommended dose (25-56 IU/KG every 3-5 days). The authors noted that the factor VIII prophylaxis randomized arm was designed to provide efficacy data to inform decision for patients unwilling to comply with the recommended dose.
ESPRIT[69] [Gringerii 2011]	Inclusion Criteria: Conducted in children aged 1 to 7 years

Supplemental NMA Methods

As described in the report, all NMAs were conducted in a Bayesian framework using the gemtc package in R.[66] An NMA extends pairwise meta-analyses by simultaneously combining both the direct estimates (i.e., estimates obtained from head-to-head comparisons) and indirect estimates (i.e., estimates obtained from common comparator[s]).[94,95]

The outcomes (rates of treated bleeding events and rates of treated joint bleeding) were analyzed using a Poisson likelihood and the log link function. The primary inputs to the NMA were the number of bleeding events and the treatment exposure time in person-years. We included two studies in our NMA: HAVEN 3 and SPINART. Data on number of bleeding events and person-years of follow-up was not reported in HAVEN 3 trial. However, these inputs were obtained from Reye 2019 (a published NMA funded by the manufacturer of emicizumab).[96] Number of treated bleeding events was reported in SPINART; we estimated the person-years of follow-up in SPINART by the treatment duration multiplied by the number of participants in the trial.

For our primary results, we used a random-effects model. We expected a priori that the random-effects model would be more appropriate because of the potential differences in populations studied. The amount of between-study variance (i.e., heterogeneity) could not be accurately estimated due to the small number of studies available. Instead, based on evidence from prior study,[96] we used informative prior for the between-study deviation is $\tau \sim$Uniform (0,0.5), which corresponds to a 'range' of treatment effects (RRs) on the multiplicative scale of ~7.10. The deviance information criteria (DIC) and residual deviance (resdev) statistics were similar for the fixed and random effects models.

Figure D.1. Network Diagram

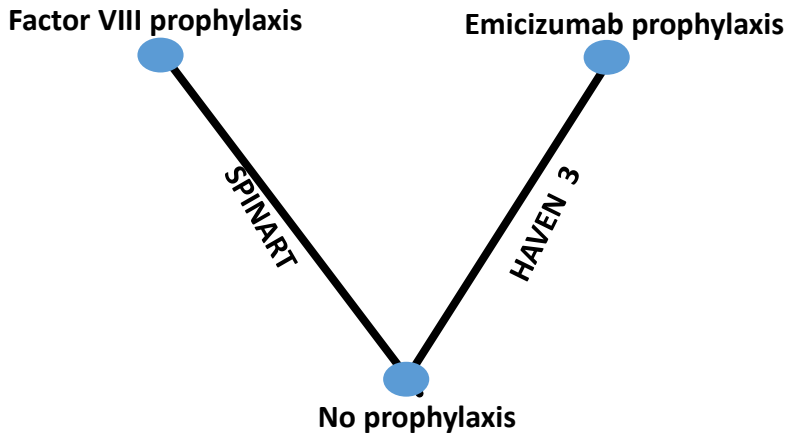


Table D5. NMA Data Inputs for Treated Bleeding Events

Study	Arm	Number of bleeds	Exposure (person-years)
HAVEN 3[21]	Emicizumab QW*	37	22.1
HAVEN 3[21]	Emicizumab Q2W*	32	22.3
HAVEN 3[21]	On-demand FVIII	369	8.18
SPINART[27,28]	FVIII prophylaxis	264	127.44
SPINART[27,28]	On-demand FVIII	4338	126.58

Table D6. NMA Data Inputs for Treated Joint Bleeding Events

Study	Arm	Number of bleeds	Exposure (person-years)
HAVEN 3[21]	Emicizumab QW*	23	22.1
HAVEN 3[21]	Emicizumab Q2W*	19	22.3
HAVEN 3[21]	On-demand FVIII	220	8.18
SPINART[27,28]	FVIII prophylaxis	242	127.44
SPINART[27,28]	On-demand FVIII	3632	126.58

QW: Once weekly dosing

Q2W: Every 2 weeks

* The two emicizumab arms were combined in the NMA

Supplemental NMA Results (Fixed Effect NMA)

Table D7. NMA Results of Annualized Treated Bleeds: Rate Ratio (95% Credible Interval)

Emicizumab		
0.57 (0.39, 0. 82)	FVIII prophylaxis	
0.03 (0.02, 0.05)	0.06 (0.05, 0.07)	On-demand FVIII

Table D8. NMA Results of Annualized Treated Joint Bleeds: Rate Ratio (95% Credible Interval)

Emicizumab		
0.53 (0.32, 0.82)	FVIII prophylaxis	
0.03 (0.02, 0.05)	0.07 (0.06, 0.08)	On-demand FVIII

Appendix E. Comparative Value Supplemental Information

Table E1. Impact Inventory

Sector	Type of Impact (Add additional domains, as relevant)	Included in This Analysis from […] Perspective?		Notes on Sources (if quantified), Likely Magnitude & Impact (if not)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health Outcomes	Longevity effects	X	X	
	Health-related quality of life effects	X	X	
	Adverse events	X	X	
Medical Costs	Paid by third-party payers	X	X	
	Paid by patients out-of-pocket	☐	☐	
	Future related medical costs	☐	☐	
	Future unrelated medical costs	☐	☐	
Informal Health Care Sector				
Health-Related Costs	Patient time costs	NA	☐	
	Unpaid caregiver-time costs	NA	☐	
	Transportation costs	NA	☐	
Non-Health Care Sector				
Productivity	Labor market earnings lost	NA	X	
	Cost of unpaid lost productivity due to illness	NA	X	
	Cost of uncompensated household production	NA	☐	
Consumption	Future consumption unrelated to health	NA	☐	
Social services	Cost of social services as part of intervention	NA	☐	
Legal/Criminal Justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	☐	
Education	Impact of intervention on educational achievement of population	NA	☐	
Housing	Cost of home improvements, remediation	NA	☐	
Environment	Production of toxic waste pollution by intervention	NA	☐	
Other	Other impacts (if relevant)	NA	☐	

NA: not applicable

Adapted from Sanders et al [97]

Table E2. List of Varied Parameters and Respective Distribution, Mean, and Standard Error

Parameter	Mean Input Value	SE	Distribution
Discount Rate	3.00%	1.28%	Beta
Bleed to Pettersson Score Conversion (Age ≥ 25)	6.520	0.130	Log Normal
Bleed to Pettersson Score Conversion (Age < 25)	36.520	0.130	Log Normal
Proportion of Joint Bleeds to Total Bleeds	0.660	0.084	Beta
Emicizumab Total Bleeds	2.600	0.130	Log Normal
Emicizumab Total Treated Bleeds	1.300	0.130	Log Normal
Emicizumab Treated Target Joint Bleeds	0.700	0.130	Log Normal
Emicizumab Treated Joint Bleeds	0.900	0.369	Log Normal
		-	-
Treated Bleeds RR (Emicizumab vs. Factor VIII)	0.570	0.190	Log Normal
Valoctocogene Year 1 Factor VIII Level	64.000	0.130	Log Normal
Treated Joint Bleed RR (Valoctocogene vs Factor VIII)	0.173	0.294	Log Normal
Child All Bleeds RR	0.273	0.130	Log Normal
Child Treated Bleeds RR	0.069	0.130	Log Normal
Average Number of Blood Days	4.500	0.496	Log Normal
Proportion of Patients Switching FVIII Range 1	1.000	0.064	Beta
Proportion of Patients Switching FVIII Range 5	0.050	0.006	Beta
Patient Weight Age 0	5.400	0.100	Normal
Patient Weight Age 0.25	7.300	0.120	Normal
Patient Weight Age 0.5	8.500	0.120	Normal
Patient Weight Age 0.75	9.700	0.160	Normal
Patient Weight Age 1	11.400	0.100	Normal
Patient Weight Age 2	14.200	0.140	Normal
Patient Weight Age 3	16.000	0.160	Normal
Patient Weight Age 4	18.500	0.180	Normal
Patient Weight Age 5	21.200	0.390	Normal
Patient Weight Age 6	23.900	0.390	Normal
Patient Weight Age 7	28.100	0.520	Normal
Patient Weight Age 8	31.500	0.580	Normal
Patient Weight Age 9	33.800	0.690	Normal
Patient Weight Age 10	40.300	1.250	Normal
Patient Weight Age 11	48.500	1.390	Normal
Patient Weight Age 12	50.600	1.440	Normal
Patient Weight Age 13	60.700	1.640	Normal
Patient Weight Age 14	65.900	1.830	Normal
Patient Weight Age 15	71.300	1.910	Normal
Patient Weight Age 16	74.400	1.210	Normal

Parameter	Mean Input Value	SE	Distribution
Patient Weight Age 17	75.100	2.080	Normal
Patient Weight Age 18	81.400	3.220	Normal
Patient Weight Age 19	78.900	2.240	Normal
Patient Weight Age 20	84.700	1.180	Normal
Patient Weight Age 30	90.200	0.780	Normal
Patient Weight Age 40	91.500	0.730	Normal
Patient Weight Age 50	90.500	0.920	Normal
Patient Weight Age 60	90.600	1.370	Normal
Patient Weight Age 70	85.800	0.920	Normal
Patient Weight Age 80	79.200	0.860	Normal
Advate (F8) Factor VIII Prophylaxis Distribution	71.15%	0.130	Dirichlet
Eloctate (F8) Factor VIII Prophylaxis Distribution	28.85%	0.130	Dirichlet
Advate (F8) Net Drug Cost	$1.14	$0.13	Log Normal
Eloctate (F8) Net Drug Cost	$1.93	$0.13	Log Normal
Emicizumab Net Drug Cost	$95.03	$0.13	Log Normal
Valoctocogene Net Drug Cost	$2,500,000	$0.13	Log Normal
Advate (F8) Furnishing Discount (%)	6.00%	0.77%	Beta
Eloctate (F8) Furnishing Discount (%)	6.00%	0.77%	Beta
Emicizumab Furnishing Discount (%)	6.00%	0.77%	Beta
Valoctocogene Furnishing Discount (%)	0.00%	0.00%	Beta
Advate (F8) Prophylaxis Drug Dosing	118.200	0.000	Normal
Eloctate (F8) Prophylaxis Drug Dosing	111.200	0.000	Normal
Advate (F8) Factor VIII On Demand Distribution	0.712	0.130	Dirichlet
Eloctate (F8) Factor VIII On Demand Distribution	0.288	0.130	Dirichlet
Advate (F8) On Demand Drug Dosing	50.400	6.429	Normal
Eloctate (F8) On Demand Drug Dosing	50.400	6.429	Normal
Cost/Bleed Age ≤ 18	$765.48	$0.13	Log Normal
Cost/Bleed 18 < Age ≤ 45	$4,604.32	$0.13	Log Normal
Cost/Bleed Age > 45	$6,858.24	$0.13	Log Normal
Surgery Costs	$44,747.17	$0.13	Log Normal
No Arthropathy Outpatient Physician Visit Rate	4.145	0.130	Log Normal
No Arthropathy Outpatient Nurse Visit Rate	2.540	0.130	Log Normal
No Arthropathy X-Ray Rate	0.485	0.130	Log Normal
No Arthropathy Computed Romography Rate	0.125	0.130	Log Normal
No Arthropathy Magnetic Resonance Imaging Rate	0.125	0.130	Log Normal
No Arthropathy Ultrasonography Rate	0.205	0.130	Log Normal
Arthropathy Outpatient Physician Visit Rate	6.630	0.130	Log Normal
Arthropathy Outpatient Nurse Visit Rate	3.840	0.130	Log Normal
Arthropathy X-Ray Rate	1.145	0.130	Log Normal

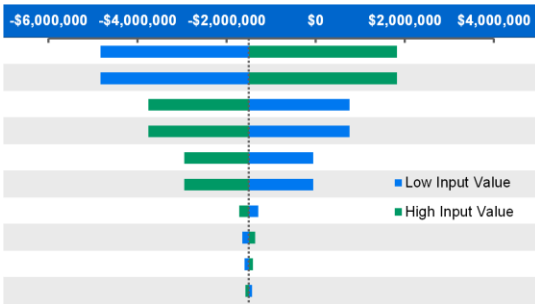
Parameter	Mean Input Value	SE	Distribution
Arthropathy Computed Romography Rate	0.240	0.130	Log Normal
Arthropathy Magnetic Resonance Imaging Rate	0.260	0.130	Log Normal
Arthropathy Ultrasonography Rate	0.500	0.130	Log Normal
Outpatient Physician Visit Cost per Resource Use	$45.77	$0.13	Log Normal
Outpatient Nurse Visit Cost per Resource Use	$23.07	$0.13	Log Normal
X-Ray Cost per Resource Use	$34.93	$0.13	Log Normal
Computed Romography Cost per Resource Use	$211.51	$0.13	Log Normal
Magnetic Resonance Imaging Cost per Resource Use	$378.23	$0.13	Log Normal
Ultrasonography Cost per Resource Use	$74.28	$0.13	Log Normal
Indirect Cost/Bleed	$1,162.28	$0.13	Log Normal
Surgery Utility	0.190	0.019	Beta
Pettersson 0 Utilities (Age ≤ 30)	0.940	0.075	Beta
Pettersson 1-12 Utilities (Age ≤ 30)	0.820	0.098	Beta
Pettersson 13-21 Utilities (Age ≤ 30)	0.820	0.098	Beta
Pettersson 22-28 Utilities (Age ≤ 30)	0.820	0.098	Beta
Pettersson 0 Utilities (30 < Age ≤ 40)	0.840	0.094	Beta
Pettersson 1-12 Utilities (30 < Age ≤ 40)	0.740	0.094	Beta
Pettersson 13-21 Utilities (30 < Age ≤ 40)	0.740	0.094	Beta
Pettersson 22-28 Utilities (30 < Age ≤ 40)	0.740	0.094	Beta
Pettersson 0 Utilities (40 < Age ≤ 50)	0.860	0.091	Beta
Pettersson 1-12 Utilities (40 < Age ≤ 50)	0.690	0.088	Beta
Pettersson 13-21 Utilities (40 < Age ≤ 50)	0.690	0.088	Beta
Pettersson 22-28 Utilities (40 < Age ≤ 50)	0.690	0.088	Beta
Pettersson 0 Utilities (50 < Age ≤ 60)	0.830	0.096	Beta
Pettersson 1-12 Utilities (50 < Age ≤ 60)	0.630	0.080	Beta
Pettersson 13-21 Utilities (50 < Age ≤ 60)	0.630	0.080	Beta
Pettersson 22-28 Utilities (50 < Age ≤ 60)	0.630	0.080	Beta
Pettersson 0 Utilities (Age > 60)	0.730	0.093	Beta
Pettersson 1-12 Utilities (Age > 60)	0.540	0.069	Beta
Pettersson 13-21 Utilities (Age > 60)	0.540	0.069	Beta
Pettersson 22-28 Utilities (Age > 60)	0.540	0.069	Beta
Treated Bleed Not Into A Target Joint Disutility	0.160	0.130	Log Normal
Target Joint Bleed Disutility	0.280	0.130	Log Normal

Table E3. Undiscounted Outcomes for the Base Case Models

Treatment	Drug Cost	Total Cost	Joint Bleeds	Treated Non-Target Joint Bleeds	Treated Target Joint Bleeds	Life Years	QALYs
Factor VIII (Model version 1 – Health Sector Perspective)	$40,021,000	$40,973,000	99.90	34.93	40.75	58.22	38.72
Valoctocogene Roxaparvovec (Model version 1 – Health Sector Perspective)	$31,804,000	$32,754,000	99.72	34.86	40.65	58.22	38.72
Factor VIII (Model version 1 – Modified Societal Perspective)	$45,307,000	$29,251,000	99.90	34.93	40.75	58.22	38.72
Valoctocogene Roxaparvovec (Model version 1 – Modified Societal Perspective)	$31,804,000	$32,842,000	99.72	34.86	40.65	58.22	38.72
Factor VIII (Model version 2 – Health Sector Perspective)	$45,307,000	$46,303,000	115.27	39.26	44.64	75.08	55.21
Emicizumab (Model version 2 – Health Sector Perspective)	$40,632,000	$41,627,000	115.27	39.26	44.64	75.08	55.21

Results use a placeholder price of $2,500,000 for valoctocogene roxaparvovec

Figure E1. Tornado Diagrams for Model Version 2: Emicizumab vs Factor VIII Incremental Modified Societal Costs



Parameter	Low Input Value	High Input Value
Emicizumab Net Drug Cost	$71.27	$118.79
Emicizumab (Month 2+) Prophylaxis Drug Dosing	1.13	1.88
Advate (F8) Net Drug Cost	$0.86	$1.44
Advate (F8) Prophylaxis Drug Dosing	88.65	147.75
Eloctate (F8) Net Drug Cost	$1.45	$2.42
Eloctate (F8) Prophylaxis Drug Dosing	83.40	139.00
Emicizumab Furnishing Discount (%)	4.50%	7.50%
Advate (F8) Furnishing Discount (%)	4.50%	7.50%
Eloctate (F8) Furnishing Discount (%)	4.50%	7.50%
Factor VIII Total Treated Bleeds	0.98	1.63

Table E4. Results of Probabilistic Sensitivity Analysis for Valoctocogene Roxaparvovec and Emicizumab versus Factor VIII

	Valoctocogene/Emicizumab		Factor VIII		Incremental	
	Mean	Credible Range	Mean	Credible Range	Mean	Credible Range
Model version 1 – Health Sector Perspective						
Total Costs	$14,748,518	[$10,019,954, $23,646,088]	$19,915,226	[$11,371,801, $30,355,213]	-$5,166,708	[-$11,547,362 $402,157]
Total QALYs	19.98	[12.67, 28.34]	19.97	[12.27, 28.33]	0.006	[-0.081, 0.099]
ICER	-	-	-	-	$1,863,748,557	[- $1,443,010,431, $1,537,678,533]
Model version 1 – Modified Societal Perspective						
Total Costs	$14,791,254	[$8,105,305, $23,704,267]	$19,959,466	[$11,395,372, $30,420,218]	-$5,168,212	[-$11,538,217 $394,585]
Total QALYs	19.98	[12.67, 28.34]	19.97	[12.27, 28.33]	0.006	[-0.081, 0.099]
ICER	-	-	-	-	$1,865,229,216	[- $1,445,126,737 $1,537,678,533]
Model version 2 – Health Sector Perspective						
Total Costs	$15,124,84	[$6,743,449, $26,984,424]	$16,814,037	[$7,605,262, $29,106,680]	-$1,689,196	[-$8,049,013, $4,182,512]
Total QALYs	25.60	[15.48, 37.73]	25.60	[15,49, 37.73]	0.005	[-0.083, 0.106]
ICER	-	-	-	-	$5,535,660	[-$660,722,763, $725,742,924]

Results use a placeholder price of $2,500,000 for valoctocogene roxaparvovec

Figure E2. Scatterplot for Model Version 1: Valoctocogene Roxaparvovec versus Factor VIII Health Sector Perspective

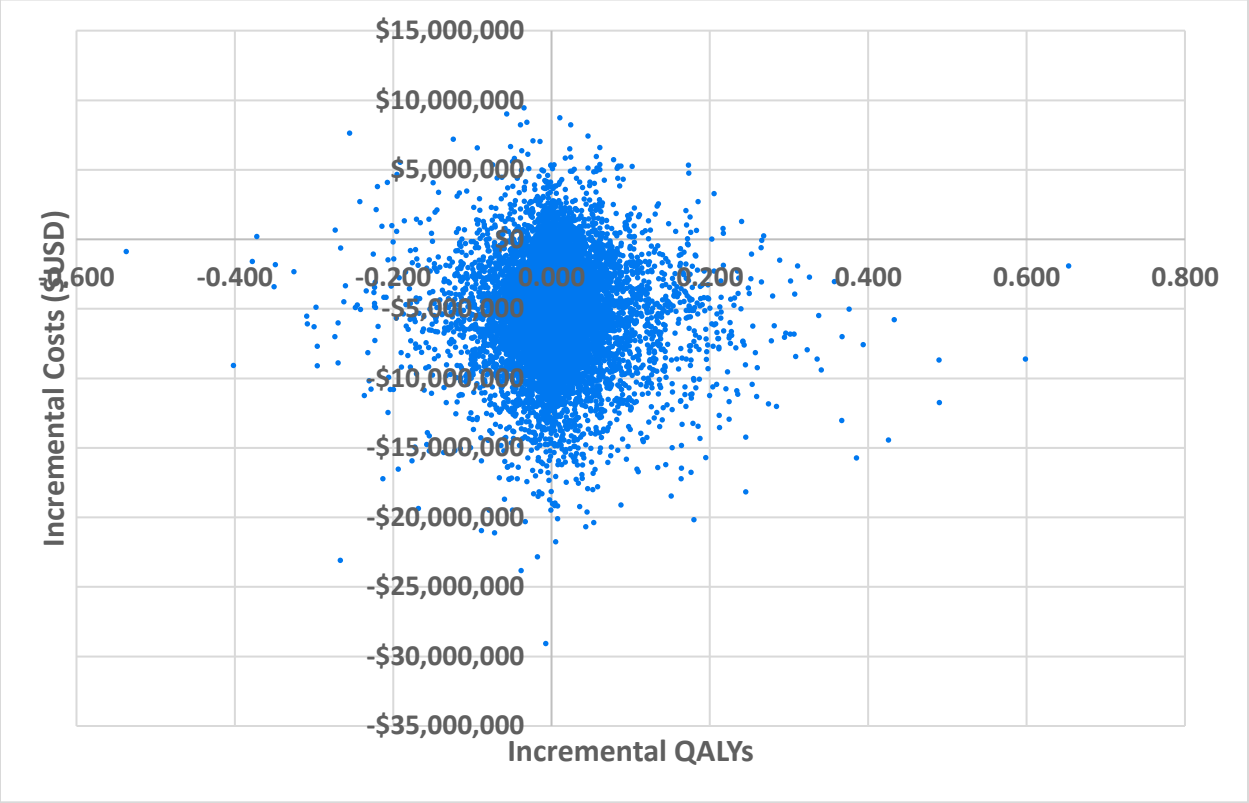


Figure E3. Scatterplot for Model Version 1: Valoctocogene Roxaparvovec versus Factor VIII Modified Societal Perspective

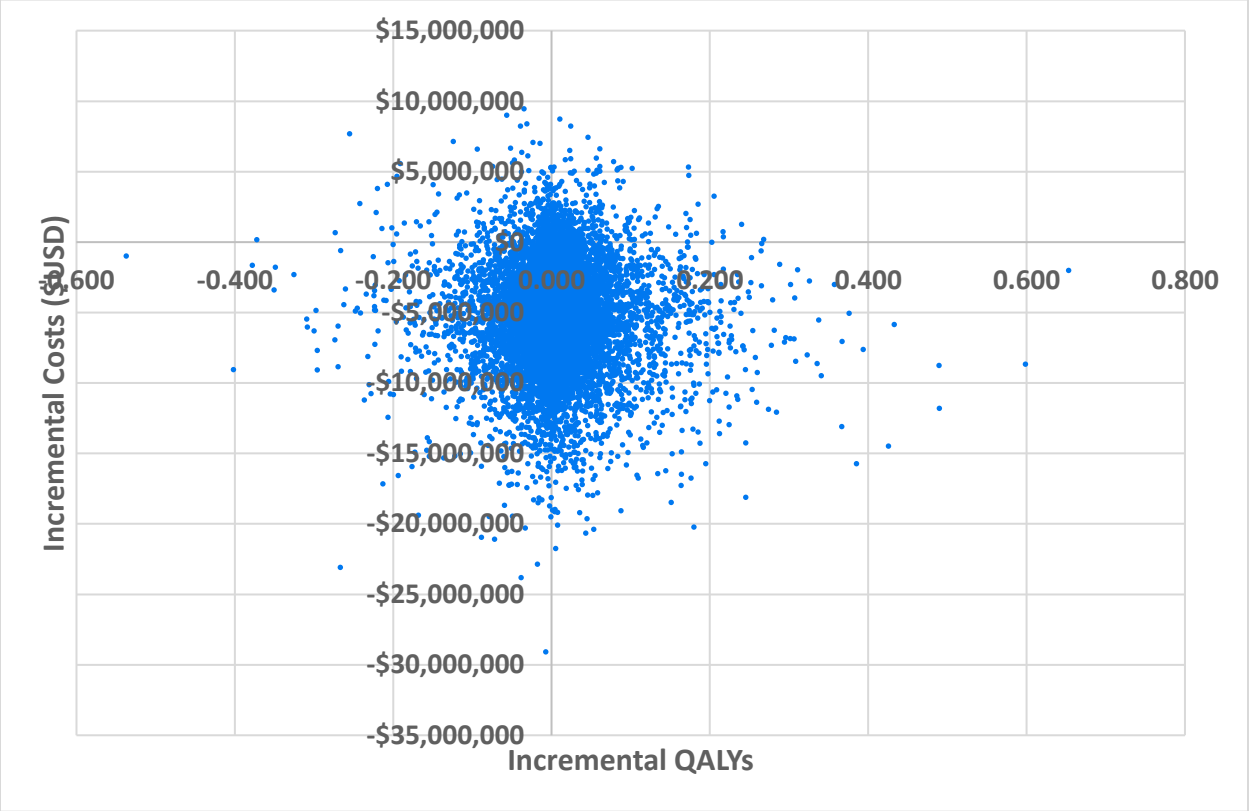


Figure E4. Scatterplot for Model Version 2: Emicizumab versus Factor VIII Health Sector Perspective

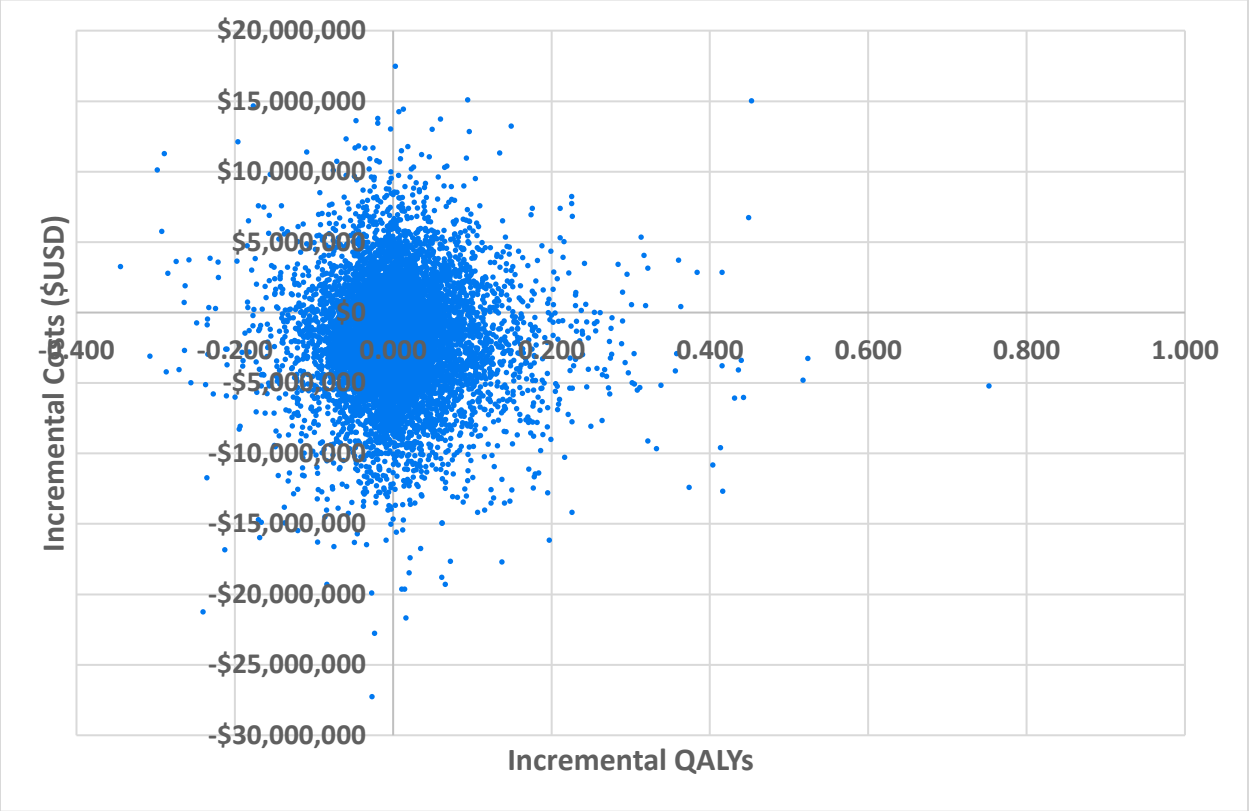


Table E5. Results of Scenario Analysis Assuming Zero Bleeds in the Factor VIII Arm in Model 1

Treatment (Perspective)	Incremental Cost	Incremental QALYs	Incremental Cost-Effectiveness Ratio
Factor VIII (Health Sector Perspective)	Reference	Reference	Reference
Valoctocogene Roxaparvovec (Health Sector Perspective)	-$4,717,000	-0.062	Cost saving, but less effect
Factor VIII (Modified Societal Perspective)	Reference	Reference	Reference
Valoctocogene Roxaparvovec (Modified Societal Perspective)	-$4,692,000	-0.062	Cost saving, but less effect

Table E6. Results of Scenario Analysis Assuming Zero Bleeds in the Factor VIII Arm in Model 2

Treatment	Incremental Cost	Incremental QALYs	Incremental Cost-Effectiveness Ratio
Factor VIII	Reference	Reference	Reference
Emicizumab	-$1,243,000	-2.055	Cost saving, but less effect

Table E7. Incremental Costs and QALYs in the SST Scenario Analyses

Scenario	Model Version	Treatment	Incremental Cost	Incremental QALYs	Incremental Cost-Effectiveness Ratio
50/50 Cost Sharing	Health Sector	Valoctocogene Roxaparvovec	$4,443,000	0.004	$1,165,851,000/QALY
	Societal	Valoctocogene Roxaparvovec	$4,452,000	0.004	$1,170,701,000/QALY
Cap Offset costs at $150,000/Year*	Health Sector	Valoctocogene Roxaparvovec	$9,129,000	0.004	$2,400,704,000/QALY
	Societal	Valoctocogene Roxaparvovec	$9,167,000	0.004	$2,410,824,000/QALY
Conservative Valoctocogene Projection	Health Sector	Valoctocogene Roxaparvovec	-$3,228,000	0.012	Dominant
	Societal	Valoctocogene Roxaparvovec	-$3,233,000	0.012	Dominant
Optimistic Valoctocogene Projection	Health Sector	Valoctocogene Roxaparvovec	-$6,073,000	0.007	Dominant
	Societal	Valoctocogene Roxaparvovec	-$6,077,000	0.007	Dominant
Payment Scenario	Health Sector	Valoctocogene Roxaparvovec	-$4,995,000	0.005	Dominant
	Societal	Valoctocogene Roxaparvovec	-$4,997,000	0.005	Dominant

Results use a placeholder price of $2,500,000 for valoctocogene roxaparvovec
*$75,000 per cycle (6-month cycles)

Appendix F. Public Comments

This section includes summaries of the public comments prepared for the New England CEPAC Public Meeting on October 30, 2020. These summaries were prepared by those who delivered the public comments at the meeting and are presented in order of delivery.

A video recording of all comments can be found here. Conflict of interest disclosures are included at the bottom of each statement for each speaker who is not employed by a pharmaceutical manufacturer. Two oral commenters did not submit their written remarks.

Ryan Hallock, LPN
Patient Advocate

My experience with being a recipient of gene therapy trials has been one of the most dynamic changes in my life. I was a severe hemophiliac B patient. Prior to December 2015, I was self-infusing two to three times a week on a prophylaxis factor regimen and treating breakthrough bleeds on an as-needed basis. These infusions could take between twenty and thirty minutes to complete and depending on my location at the time of infusing could create for socially complex situations. I had to pay copayments for this factor and other hospital needs related to my hemophilia. The breakthrough bleeds could affect one of many joints which were required for me to perform my job as a nurse. This would lead me to missing work as I was unable to perform my job duties which put me at risk for losing my job. I would have days where it physically hurt to hold my own new born daughter. All due to a breakthrough bleed.

Since participating in the gene therapy trial study, I have not had to use factor a single day. I have made many oral procedures which would require factor normally since, and in July 2019, I had an appendectomy which required no factor. This is unheard of for severe hemophilia prior to the introduction of gene therapy drugs. I have not had a single copayment for any medical interventions related to hemophilia. I have not missed a day of work related to my hemophilia status. Even more so, I am able to provide financially for my family without the worry of losing a job because of missed medical days. My family life has improved as well. I am able to be the best dad for my daughter and I have not missed a family event because of my hemophilia. I have noticed less daily pain in my own life since participating in the gene therapy study.

This is my experience of course. What changes occurred for me may not have occurred for others. It is all subjective, but when looking at this testimony of my own experience, consider the impact for others. Accessibility to a treatment option which has a long-term effect can promote financial gain for the individual for increased productivity and a decrease in cost spending related to medical

bills. Freedom from the requirements for treating the disorder should be considered as well. For myself, it was not using twenty to thirty minutes three times a week to perform a self-infusion. These treatment options are much more than simply treating a disease, but the impact of the treatment options offers freedoms and liberties to the patient.

I would like to thank those who invited me to participate in the discussion. I hope it was eye-opening and consideration for new novelty therapies is taken very seriously. Remember discussion and decisions made for the use of novelty therapies will affect many and the goal of equity in healthcare should be considered.

Ryan Hallock is a Board Member for the Mississippi Hemophilia Foundation.

Richard Ko, MD, MHS, MS
Head of Rare Blood Disorders, US Medical Affairs, Genentech, Inc.

This is an exciting time for the hemophilia community, as innovative treatment options are being developed. Genentech is proud to have partnered with the hemophilia community and to have played a leading role in advancing the treatment landscape. We appreciate this opportunity to speak to the New England CEPAC and comment on ICER's second evaluation of therapies for Hemophilia A.

Hemlibra is the first novel therapy approved in over 20 years for all persons with hemophilia A, both with and without factor VIII inhibitors. In addition to Hemlibra's established efficacy in bleed reduction, it also substantially reduces the treatment burden associated with factor replacement therapies, which includes multiple IV infusions per week. Hemlibra is administered subcutaneously and has a flexible dosing schedule allowing for injections as infrequently as every 4 weeks. This enables the long term proven benefits of continuous prophylaxis with less frequent dosing potentially increasing adherence and decreasing caregiver burden.

In this assessment, ICER concluded that Hemlibra's efficacy is comparable or better - and less costly - when compared to factor VIII prophylaxis. Today, the CEPAC panel will be voting on the effectiveness and value of Hemlibra, and we hope that you will agree that Hemlibra offers substantial long-term health and economic benefit to persons with hemophilia, healthcare providers, and the healthcare system overall. Hemlibra provides significant clinical and economic benefits as demonstrated by the totality of robust evidence from clinical trials, real-world data, network meta-analyses, and cost-effectiveness analyses. Today we will highlight the value of Hemlibra through three key points on clinical efficacy, cost-savings, and patient-centered outcomes and treatment preferences.

The clinical efficacy and safety of Hemlibra are based on the largest clinical trial program in hemophilia A to date, inclusive of patients of all ages and inhibitor status. Hemlibra has shown

meaningful reduction in overall bleeds and joint bleeds, with the majority of people in our clinical trials experiencing zero treated bleeds. Furthermore, a "before and after" comparison of 48 patients who were previously on FVIII prophylaxis in HAVEN 3, the pivotal clinical trial in people with hemophilia without inhibitors, showed that these patients experienced a 68% reduction in treated bleeds while on Hemlibra. Most importantly, the safety and efficacy outcomes are consistent between the reported real-world experience and long-term follow-up of the Hemlibra clinical trial program.

Next, when we consider the economic value that Hemlibra brings to the healthcare system, it is substantial, even by ICER's own assessment. In persons with hemophilia without inhibitors, Hemlibra is estimated to save $1.5 million over a person's lifetime compared with FVIII prophylaxis. Published cost-effectiveness analyses similarly show Hemlibra, compared to factor VIII, produces cost-offsets through potential delayed inhibitor development, lower frequency of adverse events, lower frequency of joint disease, and decreasing indirect costs from missed work. Taken as a whole, compared to FVIII, Hemlibra delivers significant value for money, throughout a person with hemophilia's lifetime.

Last, it is well known that persons with hemophilia A experience a sizable burden to their physical and mental well-being, which often extends to their families and caregivers. We have been heartened to hear testimonials regarding the benefits of Hemlibra reducing this burden due to the ease of administration, improved health-related quality of life, and increased productivity. These testimonials are backed by evidence. Real-world outcomes and preference for Hemlibra over factor VIII have been consistent with the HAVEN 3 clinical trial findings.

In closing, I would like to thank the hemophilia community for their continued partnership and deep commitment to ensuring that innovative treatments are accessible for people impacted by this condition.

Dr. Richard Ko is a full-time employee of Genentech. Inc.

Bob G. Shultz, PharmD, MS
Senior Manager – Outcome Research, Takeda Pharmaceuticals, Inc.

Takeda is committed to bringing better health and a brighter future to patients by translating science into better outcomes through the development of highly innovative medicines. Takeda has 70+ years of experience working with clinicians and patients in the bleeding disorders space, and are wholly invested in understanding and improving the lives of patients with hemophilia A.[1]

Takeda cheers innovation that brings choice and new opportunities for patients living with hemophilia. Therefore, as stakeholders in this review our role is not to choose sides, but to objectively review ICER's approaches from a scientific lens to ensure the inclusion of fair and balanced evidence, methodology, and assumptions. We understand limitations and required assumptions therefore we aim to provide feedback that is realistically addressable.

The comparative effectiveness and economic inputs that drive this model have high variability and uncertainty undermining any strong conclusions or rigid policies being taken from this report. Significant consequences on real-world clinical and economic outcomes may occur if taken too literally.

Comparative effectiveness in this review was measured by annualized bleed rates (ABRs). Clinical differentiation between prophylaxis with factor VIII (FVIII) products vs. emicizumab is not supported from the available evidence. ICER's network meta-analysis, which aggregated randomized controlled trials with important differences in study design, resulted in rate ratios (RR) with credible intervals (CI) that crossed 1 (0.22-1.47) for treated bleeds, highlighting non-inferiority between FVIII and emicizumab.[2] Notably, the RR and CI was based off efficacy data from SPINART which represents lower dosing (32.3% lower dose) and lower effectiveness compared to published real-world evidence on FVIII prophylaxis.[3,4] In fact, recent research cited by ICER illustrated FVIII prophylaxis resulting in lower ABRs in the real-world compared to emicizumab's ABRs in HAVEN [3.4,5] Efficacy and effectiveness should not be compared, however, this circumstance was created when ICER used more contemporary 'real-world' dosing instead of dosing from the clinical trial. Additionally, personalized-dosing and pharmacokinetic (PK) guided dosing was not in the scope of this review, however, it occurs in the real-world and can further optimize the clinical benefits of FVIII therapy and should be considered contextually for comprehensiveness.[6] In summary of the comparative effectiveness review, available evidence isn't conclusive of clinical differentiation between products due to limitations in study designs and lack of strong evidence. Prophylaxis with either treatment option has been shown to be more effective at reducing ABRs compared to on-demand treatment, but differentiation of effectiveness amongst them is not discernable.[3,4,5]

Emicizumab showed cost-savings at its current price in the base-case configuration of ICER's model, however, a biased FVIII dosing assumption that was generalized to all patients contradicts the conclusions. Labeled dosing for ADVATE (Antihemophilic Factor [Recombinant]) prophylaxis in

adults ranges from 60-160 IU/kg/week. While averages help inform population-based decisions, it may be inappropriate to generalize an average dose as being representative for a treatment that is highly personalized.[6,7] Also, the dosing used by ICER from the ATHN database represents the starting prescribed dose. Lack of adherence or changes in dose over time is not included in starting prescribed dose and is therefore not real-world. In fact, ICER cites that only 50-70% of FVIII patients are adherent to their prescribed FVIII regimen yet assumed 100% adherence to the prescribed regimen.[2,8,9] An 11% decrease in consumption from prescribed FVIII dose, whether due to adherence or dose change, results in FVIII becoming cost-savings compared to emicizumab.

It is unbalanced to incorporate additional cost-consequences from real-world practice with FVIII (e.g. increased doses) without incorporating real-world cost-consequences from emicizumab (e.g. product wastage). Emicizumab wastage increases the costs associated with emicizumab treatment and is a real-world consequence due to fixed vial containers. Research shows an increase in costs of up to 7.8% due to emicizumab wastage.[10] Failure to include real-world cost-consequences for both therapies is an unfair cost-comparison. In summary, emicizumab's long-term value for money at the current price is uncertain due to individual differences between patients and high variability/uncertainty around sensitive dosing parameters in the model.

Takeda is committed to serving patients with hemophilia A. Takeda believes the decision for which therapy is most appropriate for each patient should be made at the patient and physician level. Cost-effectiveness, in hemophilia A especially, is dynamic and should more flexible than ICER's current interpretation of their model. Individual payers may have different conclusions based on their specific population and real-world costs. We appreciate the opportunity to deliver this oral comment and hope to have contributed to the full understanding of this report by scientifically uncovering limitations that may have led to biases.

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Dr. Bob Shultz is a full-time employee of Takeda Pharmaceuticals.

Jennifer Sleboda
Patient Advocate

I have a 5-year old son with severe hemophilia A without inhibitors, and he's been on Hemlibra since April 2019. Previously, he was on Factor VIII (Advate) for over three and a half years, which he got through a broviac catheter as an infant and then port infusions every other day; his port was removed last July.

Why we chose to switch to Hemlibra:

Our son had a port put in when he was a year old. When he turned 4, we were told that there were signs of thrombosis – prominent blue veins in his upper chest and arm – so we needed to get the port removed sooner than later.

Hemlibra had been approved about five months previously. I had no desire to do peripheral infusions (sterile procedure) and stick my child with a needle every other day. I had been dreading peripheral infusions since the day I learned he had hemophilia. It was a no-brainer for us – a sub-cutaneous injection every two weeks vs. peripheral infusions every other day.

Our son did well on Factor VIII, fortunately, but Hemlibra provides consistent protection. No varying levels of protection due to the short half-life and troughs before the next infusion, which are windows of risk for bleeds. Less worry, less anxiety.

As a parent, the benefits of Hemlibra fall under one main category: decreased treatment burden.

Ports are convenient for Factor VIII therapy, but there is always an infection risk. Having to take your child to the ER every time he has a fever over 100.3 is unreasonable, stressful, and time-consuming – because young children get fevers all the time. You spend 3-5 hours at the ER each time, and your child gets antibiotics every time, whether or not s/he has a bacterial infection. The next day, you have to take him/her back to get the second dose. Then every time, at least in our case, we found out it was a virus.

Infusing a toddler or preschooler every other morning is a lot of work, because they don't want to sit still, and they don't like the procedure. This requires a 2-person team. My husband and I both had to travel for work. When one of us traveled, we would have to arrange for a homecare nurse to help the one who was home with our son, which was of course an extra insurance cost.

Infusing a toddler or preschooler is a hassle and time-consuming, especially because it's a sterile procedure – trying to keep everything sterile can be a challenge when you have a squirmy, uncooperative kid. If something gets contaminated by accident, you have to start over again with fresh supplies. Before infusing, you have to apply numbing cream to the skin over the port 20-30 minutes in advance. Occasionally, I'd forget to put it on, which delays the infusion. Sometimes we would miss the port with the needle (once, twice) and have to start all over again with a new needle and supplies. These situations would often make us late to work.

Overall, Hemlibra has been a life-changer for us. No more port, no more worry about infections and thrombosis, no more trips to the ER when he has a fever, no more unnecessary antibiotics, and no more infusions every other morning. And importantly, much less anxiety and worry knowing that our son has consistent protection. (Since we haven't been trained to give peripheral infusions, if our son does have a bleed on Hemlibra, we take him to our local hemophilia treatment center to have a nurse do the Factor VIII infusion.)

I should mention that I've talked to a number of parents who have young children with hemophilia through a hemophilia moms' group, a parents' support group, and our local hemophilia association. Without exception, all of the parents I've spoken to – who have switched from factor to Hemlibra – have expressed the same challenges with ports and factor, the same reasons for switching to Hemlibra, and describe Hemlibra as a "life-changer" – especially those whose kids were having bleeds on factor, because since switching, the bleeds have stopped.

Thank you for this opportunity to provide testimony.

Jennifer Sleboda is a Board Member of the Hemophilia Association of the Capital Area, which receives funding from pharmaceutical and home care companies.

Len Valentino, MD
President & Chief Executive Officer, National Hemophilia Foundation

On behalf of the National Hemophilia Foundation, I want to express my sincere appreciation for the work ICER has done to support the treatment of people with inherited bleeding disorders.
I am a pediatric hematologist with over thirty years of experience caring for people with hemophilia and other bleeding disorders. My career path has taken me from academic medicine into the biopharmaceutical industry and drug development including gene therapy for hemophilia. For the past nine months have had the privilege of serving the bleeding disorders community as the President and Chief Executive Officer of the National Hemophilia Foundation.

As the ICER panel understands, hemophilia is a congenital hemorrhagic disorder in which bleeding into the joints accounts for over 90% of all serious bleeding along with muscle and soft tissue bleeding as well as bleeding into the brain. Bleeding is directly related to decrements in health related quality of life and excess healthcare utilization and increased cost of care.
Historically, the focus has been on boys and men with severe hemophilia, however, recently, attention has also been focused onto patients with non-severe disease and women who are also affected by bleeding and may develop joint disease.

Bleeding, including joint bleeding, has traditionally been the outcome most closely assessed to judge effectiveness of treatment. However, given the transformative nature of the therapies under consideration here, as well as the numerous ways that hemophilia impacts an affected person and his or her family and caregivers, other patient important outcomes including joint pain, limitations in activities, lost time from school or work, emotional well-being, psychological stress related to anticipation of bleeding especially with activities, and of course, the cost of bleeding to the healthcare system must be considered to demonstrate benefit to patients, their families and society. Bleeding is no longer the sensitive outcome capable of differentiating products and manufacturers must focus on the previously stated patient-important endpoints to demonstrate value to patients. That said, over the lifetime of a patient, every bleeding event matters, including microhemorrhage or subclinical bleeding into joints. Achieving sustained protection at a higher level and eliminating periods of low levels may reduce or eliminate these problematic silent hemorrhages thereby improving outcomes for patients.

Hemophilia is associated with a significant burden of disease and treatment not only for the patient but also for caregivers. The paradigm-shifting therapies at the center of this evaluation by ICER have the real possibility of lessening or eliminating that burden and freeing patients and their families to thrive, unencumbered by hemophilia.

These novel therapies introduce a new set of complexities that must be dealt with on an ongoing basis including clinical, psychological and laboratory monitoring of patients which require expertise currently only available in the coordinated care network afforded by the federally funded hemophilia treatment centers, considered to be the gold standard for chronic disease management. These experts in medicine, nursing, physiotherapy, social services and pharmacy management optimize patient outcomes over the lifespan of people with bleeding disorders while ensuring the cost effectiveness of the care. Working side by side, the healthcare professionals in the hemophilia treatment centers along with their patients and families utilize a model of shared decision making to inform, educate and empower people with bleeding disorders to make personalized choices regarding their care while affording access to all approved therapies. All treatment options should be available to patients, without barriers due to cost, short-sighted utilization management strategies, narrow formularies or restrictive provider networks and the price of products should be fair and reasonable so as to not affect adequate and timely access to therapy.

NHF and the entire bleeding disorders community look forward to generating additional new real world data to demonstrate the value of these paradigm-shifting, transformative therapies to not only better inform ICER's economic modeling and analysis but to preserve access to these lifechanging treatments for all people with bleeding disorders.

On behalf of the bleeding disorders community, I wish to thank you for the opportunity to address ICER and provide these comments.

The National Hemophilia Foundation is a 501c3 organization that receives program and educational grant funding from manufacturers of hemophilia products to support their mission.

Sonji Wilkes
Senior Director, Policy, Advocacy & Government Education, Hemophilia Federation of America

Hemophilia Federation of America is a community-based, grassroots organization, dedicated to improving care and quality of life for people with bleeding disorders by removing barriers to safe and effective treatment.

At the outset, we emphasize that HFA doesn't advocate on behalf of any given product. Hemophilia's complexity; direct and indirect burdens on patients (PWH) and caregivers; the variations among PWHs; and the potential risks of any novel therapy – all demand an individualized, patient-centric approach to assessment and treatment.

In 2020, the hemophilia community is closer than ever to long-sought, more effective and less burdensome treatment options. However, our optimism about emerging treatments is tempered by memories of our community's devastating history with HIV- and hepatitis C- tainted products – as well as by continuing concern over hemophilia's financial toxicity. Demonstrating value, in all its dimensions, will be important for patient access and patient confidence.

As in our October 30th comments, HFA will focus on: current prophylaxis regimens; the potential other benefits offered by novel therapies; and caution about assessing value where very substantial unknowns exist with respect to a treatment's risk-benefit profile.

Current standard of care for hemophilia A.
HFA appreciates that ICER incorporated utilization data based on real world treatment regimens. As HFA and NHF noted in earlier written comments, there is substantial clinical consensus that prophylaxis needs to, and currently does, aim for trough levels above 1% in order to achieve desired health outcomes and meet contemporary treatment guidelines.
The discussion of present-day prophylaxis regimens highlights just how important it is to include real world data on utilization and patient outcomes in value assessments. Patient organizations and treaters have made, and continue to make, concerted efforts to contribute to this body of data, but there is still more to be done, including on the part of drug sponsors, to develop the necessary evidence base.

HFA remains concerned about incidental remarks in the report that may be read as questioning the value of dosing at current standard levels. We agree that FVIII prophylaxis is expensive – and are always mindful that many patients struggle with ongoing financial toxicity due to yearly out of pocket expenses. Please know that PWHs understand how expensive their care is, and seek to be

responsible in their care decisions. At the same time, patients have the least leverage of anyone in the ecosystem to bring down spending for medically necessary care, let alone drug prices. And effective bleed control for PWHs is non-negotiable: it cannot be compromised by utilization management in an effort to bring down drug prices.

"Potential Other Benefits and Contextual Considerations"

We appreciate that ICER recognizes that the novel treatments under review advance many patient-important outcomes above and beyond annual bleed rates. Direct and indirect evidence of those benefits is indeed stronger than ICER credits, including evidence showing that easier and less frequent administration of therapy will likely improve patient adherence, and evidence showing that better adherence and consistently higher factor activity levels in turn contribute to improved outcomes. These include avoidance of bleeds and microbleeds, which benefits long-term, baseline joint health and overall quality of life. The evidence also shows that these novel treatments have significant positive impacts on family life, school, work, and more.

HFA argues that these benefits are NOT "statistically non-significant." Rather, patient preferences documented in HAVEN 3 and 4 (e.g.), powerfully suggest that patients experienced significant improvements in their quality of life from their migration to the novel treatment.

Concern about finding of "dominance"

ICER concludes that gene therapy is likely to be "a dominant treatment" when measured against factor VIII prophylaxis. HFA cautions that this finding is susceptible to misreading. We understand that ICER uses "dominance" in the context of price only. But from a patient's perspective, we have to stress that the unknowns around variability, durability, and potential long-term harms from such novel therapies must figure into any assessment informing treatment and coverage decisions. ICER should make clear that its preliminary findings of dominance are not intended to shape such decisions. Given the unpredictable nature of breakthrough bleeding, payers should also be reminded that continued access to clotting factor will still be needed.

Conclusion

The choice of treatment for each patient with hemophilia needs to be individualized, patient-centric, accessible and affordable. The full range of products (including clotting factor, non-factor therapies, and eventually gene therapies) must be available for patients, and patients, working in consultation with their doctors, must be empowered to develop treatment plans that best preserve their health and quality of life.

Hemophilia Federation of America receives manufacturer support, consulting fees and honoraria from Takeda, Genentech, Bayer, CSL Behring, Novo Nordisk, Sanofi Genzyme, HEMA Biologics, Kedrion BioPharma, Pfizer, Aptevo, BioMarin, Grifols, Octapharma, Spark Therapeutics, UniQure, Siaglon Therapeutics, PCORI.

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

On behalf of BioMarin, I appreciate the opportunity to participate in the Institute for Clinical & Economic Review (ICER)'s review for "Valoctocogene Roxaparvovec and Emicizumab for Hemophilia A: Effectiveness and Value."

In December 2019, BioMarin submitted a Biologics License Application to the U.S. Food and Drug Administration (FDA) for valoctocogene roxaparvovec, for adult males with severe hemophilia A. The FDA granted valoctocogene roxaparvovec Breakthrough Therapy and Orphan Drug designations. This August, BioMarin received a Complete Response Letter in which the FDA raised a new recommendation for two years of data from our ongoing Phase 3 study. The Agency did not identify any new safety concerns. While BioMarin is disappointed that patients will not have access to this therapy at this time, we remain committed to collaborating with the FDA in order to submit a more complete dataset from our ongoing clinical trials. We appreciate that ICER recognizes the potentially transformative nature of valoctocogene roxaparvovec for hemophilia A and are pleased that ICER's preliminary analyses highlight the potential of valoctocogene roxaparvovec to improve outcomes and reduce healthcare costs.

For patients with severe hemophilia, World Federation of Hemophilia guidelines recommend "regular long-term prophylaxis as the standard of care to prevent hemarthrosis and other spontaneous and breakthrough bleeding, maintain musculoskeletal health, and promote quality of life" . Prophylaxis with Factor VIII (FVIII) requires replacement products 2-3 times per week or 100-150 infusions per year. Despite these burdensome regimens, many people continue to experience breakthrough bleeds, resulting in progressive and debilitating joint damage. There is significant clinical consensus that micro-bleeding, breakthrough bleeding, and other negative sequelae often result in a negative impact on patients' quality of life. Additional challenges faced include treatment intensity, frequent venous access issues, high cost of therapies, access to treatment centers and insurance coverage, often leading to suboptimal adherence of current therapies. Poor adherence to therapy could further compromise outcomes, increase costs and lead to substantial burden not only for the persons with hemophilia, but also their families, caregivers, healthcare systems and

communities. While the introduction of emicizumab has provided another option for patients, chronic therapy with subcutaneous injections is still required.

Valoctocogene roxaparvovec is an adeno-associated virus (AAV)-based gene therapy for hemophilia A designed to enable sustained production of the missing FVIII protein after a one-time infusion. The objective of controlling bleeding without the need for FVIII prophylaxis could address major unmet patient needs while sparing the treatment burdens of chronic therapies for hemophilia A. It is the largest gene therapy clinical development program in hemophilia A, with 5 clinical trials underway. Our phase 3 study is fully enrolled with 134 participants dosed and is powered to demonstrate superiority over prophylaxis FVIII treatment on the primary endpoint, annualized bleeding rate (ABR). With the significant amount of data that continues to be collected, we are confident that valoctocogene roxaparvovec has the potential to address major unmet needs and provide a paradigm shift in the treatment of severe hemophilia A.

Comments addressing ICER's clinical and economic review have been provided previously and BioMarin is pleased to see that ICER has incorporated some of these recommendations into the final report. We are also pleased to read ICER's conclusion that valoctocogene roxaparvovec is dominant in comparison to FVIII treatment. For future reviews, BioMarin encourages ICER to continue to work with stakeholders in order to evolve its current value framework so that clinically important and patient-relevant benefits, such as those listed in coreHEM, could be embedded. This would provide additional contextual benefits as core elements in a quantitative value framework.

With more than 20 years of innovation, BioMarin is one of a few pioneering biotechnology companies to exclusively develop therapies for rare and ultra-rare diseases. Our significant focus on research is driven by our patients, and we invest nearly half of our revenue into R&D and is are dedicated to supporting access for patients in need of our therapies through a range of programs. BioMarin is committed to leading the way to the first ever gene therapy in hemophilia A, and we will continue to work with stakeholders to ensure patients who may benefit from our innovation have access to it.

Dr. Wing Yen Wong is a full-time employee of BioMarin.

Appendix G. Conflict of Interest Disclosures

Tables G1 through G3 contain conflict of interest (COI) disclosures for all participants at the October 30 Public meeting for the New England CEPAC.

Table G1. ICER Staff and Consultants and COI Disclosures

ICER Staff and Consultants	
Foluso Agboola, MBBS, MPH,* Director, Evidence Synthesis, ICER	**Cat Koola, MPH**, * Program Manager, ICER
Pamela Bradt, MD, MPH,* Chief Scientific Officer, ICER	**Steven D. Pearson, MD, MSc**,* President, ICER
Rick Chapman, PhD, MS,* Director of Health Economics, ICER	**David M. Rind, MD, MSc**,* Chief Medical Officer, ICER
Monica Frederick,* Program and Event Coordinator, ICER	**Danny Quach, PharmD**,* University of Illinois at Chicago College of Pharmacy
Serina Herron-Smith,* Research Assistant, ICER	**Surrey M. Walton, PhD**,* Associate Professor, Pharmacy Systems, Outcomes and Policy Assistant Director, Center for Pharmacoepidemiology and Pharmacoeconomic Research University of Illinois at Chicago College of Pharmacy

*No conflicts of interest to disclose, defined as individual health care stock ownership (including anyone in the member's household) in any company with a product under study, including comparators, at the meeting in excess of $10,000 during the previous year, or any health care consultancy income from the manufacturer of the product or comparators being evaluated.

Table G2. New England CEPAC Panel Member Participants and COI Disclosures

Participating Members of New England CEPAC	
Robert H. Aseltine, Jr., PhD (Chair)* Professor and Chair, Division of Behavioral Sciences and Community Health Director, Center for Population Health	**Kimberly Lenz, PharmD (ex-officio)*** Clinical Pharmacy Manager MassHealth
Rena Conti, PhD* Associate Research Director of Biopharma and Public Policy, Institute for Health System Innovation and Policy; Associate Professor, Questrom School of Business	**Greg Low, RPh, PhD*** Program Director, MGPO Pharmacy Quality and Utilization Program
Megan Golden, JD** Co-Director, Mission:Cure	**Eleftherios Mylonakis, MD, PhD, FIDSA*** Chief of the Infectious Diseases Division and Dean's Professor of Medicine, Warren Alpert Medical School of Brown University
Claudia B. Gruss, MD, FACP, FACG* Gastroenterologist and Internist, Western Connecticut Medical Group	**Stephanie Nichols, PharmD, BCPS, BCPP, FCCP*** Associate Professor of Pharmacy Practice University of New England College of Pharmacy
Claudio W. Gualtieri, JD* Advisor, Center to Champion Nursing in America	**Leslie Ochs, PharmD, PhD, MSPH*** Associate Professor of Social and Administrative Pharmacy, University of New England College of Pharmacy
Rebecca Kirch, JD* Executive Vice President, Health Care Quality and Value for the National Patient Advocate Foundation (NPAF)	**Jeanne Ryer, MSc, EdD*** Director, NH Citizens Health Initiative
Stephen Kogut, PhD, MBA, RPh* Professor of Pharmacy Practice University of Rhode Island College of Pharmacy	**Jason L. Schwartz, PhD*** Assistant Professor Department of Health Policy and Management, Yale School of Public Health
Tara Lavelle, PhD* Assistant Professor Center for the Evaluation of Value and Risk in Health at Tufts Medical Center	**Jason H. Wasfy, MD, MPhil*** Director, Quality and Outcomes Research, Massachusetts General Hospital Heart Center Medical Director, Massachusetts General Physicians Organization

*No conflicts of interest to disclose, defined as individual health care stock ownership (including anyone in the member's household) in any company with a product under study, including comparators, at the meeting in excess of $10,000 during the previous year, or any health care consultancy income from the manufacturer of the product or comparators being evaluated.

** Mission: Cure has received grants from AbbVie for patient education and charitable support.

Table G3. Policy Roundtable Participants and COI Disclosures

Policy Roundtable Participant	Conflict of Interest
Leslie Fish, RPh, PharmD, Vice President of Clinical Pharmacy, IDP Analytics	No financial conflicts to disclose.
Richard Ko, MD, MHS, MS, Head of Rare Blood Disorders, US Medical Affairs, Genentech, Inc.	Dr. Richard Ko is a full-time employee of Genentech, Inc.
Brian O'Mahony, Chief Executive, Irish Haemophilia Society, Patient Advocate	Brian O'Mahony has received fees for participation in advisory boards or educational activities from Bayer, BioMarin, Freeline, Roche and Uniqure.
Steven Pipe, MD, Pediatric Medical Director, Hemophilia and Coagulation Disorders Program, University of Michigan	Dr. Steven Pipe has received consulting fees from Apcintex, Bayer, BioMarin, Catalyst Biosciences, CSL Behring, HEMA Biologics, Freeline, Novo Nordisk, Pfizer, Roche/Genentech, Sangamo Therapeutics, Sanofi, Takeda, Spark Therapeutics, uniQure.
Margaret Ragni, MD, MPH, Professor of Medicine and Clinical and Translational Medicine, University of Pittsburgh	Dr. Margaret Ragni receives research funding (through the University of Pittsburgh) for gene therapy trials with SPARK, a gene therapy trial with BioMarin, and past gene therapy trial funding with Sangamo.
Mark Skinner, JD, President & CEO, Institute for Policy Advancement Ltd, Patient Advocate	*
Wing Yen Wong, MD, Group Vice President, Global Medical Affairs, BioMarin Pharmaceutical Inc	Dr. Wing Yen Wong is a full-time employee of BioMarin Pharmaceuticals.
John Watkins, PharmD, MPH, BCPS Formulary Manager, Premera Blue Cross	Dr. John Watkins is a full-time employee of Premera Blue Cross.
Todd Williamson, PhD, MSc, Vice President, Data Generation & Observational Studies, Bayer	Dr. Todd Williamson is a full-time employee of Bayer Pharmaceuticals.

*Mr. Skinner has received fees and honoraria of more than $5,000 for educational presentations and advisory board participation from F. Hoffman-La Roche / Genentech, Bayer Healthcare, BioMarin, and the Blue Cross Blue Shield Association. Mr. Skinner's household has or held equity interests in the following companies in the health sector: Cryosport, CVS Health, Editas Medicine, Horizon discovery, Illumina, Intellia Therapeutics, Intuitive Surgical, Johnson & Johnson (Sold), Novartis, Regeneron (Sold) and Teladoc Health. These holdings are independently managed by a financial advisor with instructions not to invest in companies with a known interest in therapies for bleeding disorders. Mr. Skinner is a member of the ICER Governing Board; Board of Directors of the World Federation of Hemophilia USA, which receives product and monetary donations for a global humanitarian aid program; serves as a consultant for the US National Hemophilia Foundation, and is a member of the NHF Scientific Advisory Council. Mr. Skinner is a Principal investigator for the Patient-Reported Outcomes and Burdens and Experiences (PROBE) study, which has received fees and grant support from Bayer, BioMarin, CSL-Behring, Freeline Therapeutics, Novo Nordisk, F. Hoffman-La Roche, Sanofi, Sobi, Takeda, uniQure. The PROBE study is an independent, investigator-led research project led by patients and patient advocacy organizations. Mr. Skinner is a person with severe hemophilia A.