Emicizumab for Hemophilia A with Inhibitors: Effectiveness and Value

Final Evidence Report

April 16, 2018

Prepared for

ICER Staff	University of Washington School of Pharmacy Modeling Group
David Rind, MD Chief Medical Officer Institute for Clinical and Economic Review **Foluso Agboola, MBBS, MPH** Research Scientist Institute for Clinical and Economic Review **Varun Kumar, MBBS, MPH, MSc** Health Economist Institute for Clinical and Economic Review **Celia Segel, MPP** Program Manager Institute for Clinical and Economic Review **Rick Chapman, PhD, MS** Director of Health Economics Institute for Clinical and Economic Review **Alexandra Ellis, MSc, AM** Senior Scientist, HTA and Economic Evaluation Institute for Clinical and Economic Review **Daniel A. Ollendorf, PhD** Chief Scientific Officer Institute for Clinical and Economic Review **Steven D. Pearson, MD, MSc** President Institute for Clinical and Economic Review	**Lotte Steuten, MSc, PhD** University of Washington **Gregory Guzauskas, MSPH, PhD** University of Washington

DATE OF PUBLICATION: April 16, 2018

David Rind served as the lead author for the report. Foluso Agboola led the systematic review and authorship of the comparative clinical effectiveness section. Varun Kumar and Rick Chapman were responsible for oversight of the cost-effectiveness analyses and developed the budget impact model. Celia Segel authored the section on coverage policies and clinical guidelines. Alexandra Ellis, Dan Ollendorf, and Steven Pearson provided methodologic guidance on the clinical and economic evaluations. The role of the University of Washington (UW) School of Pharmacy Modeling Group is limited to the development of the cost-effectiveness model, and the resulting ICER reports do not necessarily represent the views of the UW. We would also like to thank Molly Morgan, Aqsa Mugal, Erin Lawler, and Matt Seidner for their contributions to this report.

About ICER

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The funding for this report comes from government grants and non-profit foundations, with the largest single funder being the Laura and John Arnold Foundation. No funding for this work comes from health insurers, pharmacy benefit managers, or life science companies. ICER receives approximately 20% of its overall revenue from these health industry organizations to run a separate Policy Summit program, with funding approximately equally split between insurers/PBMs and life science companies. For a complete list of funders and for more information on ICER's support, please visit http://www.icer-review.org/about/support/.

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The findings contained within this report are current as of the date of publication. Readers should be aware that new evidence may emerge following the publication of this report that could potentially influence the results. ICER may revisit its analyses in a formal update to this report in the future.

Acknowledgements

In the development of this report, ICER's researchers consulted with several clinical experts, patients, manufacturers, and other stakeholders. The following clinical experts provided input that helped guide the ICER team as we shaped our scope and 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-stakeholder-list/.

Expert Reviewers

Steven Pipe, MD
Professor of Pediatrics and Communicable Diseases; Professor of Pathology
University of Michigan
Dr. Pipe has disclosed receipt of consulting fees in excess of $5,000 from the following life sciences companies: Bayer, BioMarin, Bioverativ, CSL Behring, Novo Nordisk, Pfizer, Roche, Shire, uniQure. In addition, Shire has sponsored basic research conducted by Dr. Pipe.

Margaret V. Ragni, MD, MPH
Professor of Medicine, Division of Hematology/Oncology, University of Pittsburgh; Director, Hemophilia Center of Western PA
No relevant conflicts of interest to disclose, defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers

Mark W. Skinner, JD
President and CEO, Institute for Policy Advancement Ltd.; Past President (2004-2012), World Federation of Hemophilia; President, World Federation of Hemophilia USA
Mr. Skinner has disclosed the following relationships:

- *Honoraria > $5,000: Mr. Skinner has received honoraria for educational presentations and advisory board participation with F. Hoffman-La Roche, Bayer Healthcare, and the Blue Cross Blue Shield Medical Advisory Panel.*
- *Equity Interests > $10,000: Mr. Skinner's household has equity interests in the following companies: CVS, Foundation Medicine, Illumina, Intuitive Surgical, Merck, Novartis, Regeneron. These holdings are managed by a financial advisor with instructions not to invest in companies with a known interest in therapies for bleeding disorders.*
- *Positions: Mr. Skinner is the president of World Federation of Hemophilia USA, which receives product and monetary donations for a humanitarian aid program, serves as a*

consultant for the US National Hemophilia Foundation, and is a member of the NHF Scientific Advisory Council.

- *Research: Mr. Skinner is a Principal investigator for the Patient-Reported Outcomes and Burdens and Experiences (PROBE) study, which is funded with grant support from Baxalta (part of Shire), Bayer, Bioverativ, CSL Behring, Novo Nordisk, Roche, Sobi. The PROBE study is an independent, investigator-led research project led by patients and patient advocacy organizations.*
- *Personal: Mr. Skinner is a person with severe hemophilia A.*

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List of Acronyms Used in this Report

ABR	Annualized bleeding rate
AE	Adverse event
AHRQ	Agency for Healthcare Research and Quality
aPCC	Activated prothrombin complex concentrate
aPTT	Activated partial thromboplastin time
ASP	Average sales price
BI	Budget impact
BPA	Bypassing agent
BU	Bethesda unit
CI	Confidence interval
CID	Clinically-important difference
CMS	Centers for Medicare and Medicaid Services
Ctrough	Plasma trough concentration
EQ-5D-5L	EuroQol 5-dimension Self Report Questionnaire
FDA	United States Food and Drug Administration
Haem-A-QoL	Hemophilia Quality of Life Questionnaire for Adults
HTC	Hemophilia treatment center
ITI	Immune tolerance induction
NIS	Non-interventional study
NHF	National Hemophilia Foundation
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality-adjusted life year
RCT	Randomized controlled trial
RR	Relative risk
rFVIIa	Recombinant activated factor VII
SAE	Serious adverse event
TMA	Thrombotic microangiopathy
Tx	Treatment
US	United States
USPSTF	US Preventive Services Task Force
VAS	Visual analogue scale
WAC	Wholesale acquisition cost
WFH	World Federation of Hemophilia
WTP	Willingness to pay

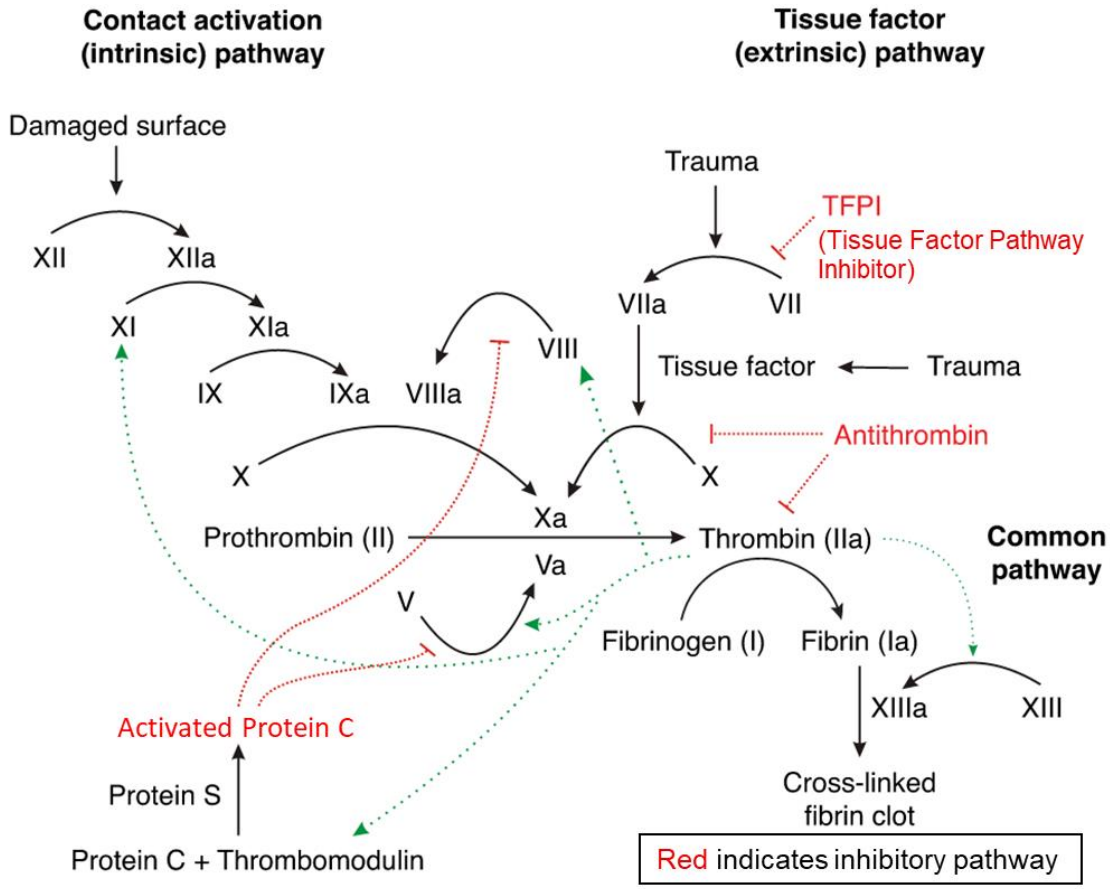
Executive Summary

Background

Hemophilia A

Hemophilia A is a condition of increased tendency to bleed due to an inherited deficiency of factor VIII, which disrupts the clotting cascade (Figure ES1). Hemophilia A has X-linked recessive inheritance, and so predominantly affects males. It is the most common form of hemophilia with an incidence of one in 5,000 male births.[1]

Figure ES1. 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.

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 typically administer 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.

Factor Inhibitors

Approximately one-quarter of patients with severe hemophilia A who receive factor VIII concentrates develop neutralizing antibodies known as "inhibitors."[5] The total population of patients in the US with hemophilia A and inhibitors is estimated to be around 950.[6] Inhibitors neutralize infused factor VIII, rendering it ineffective for prophylaxis (i.e., prevention) and on-demand treatment. The presence of inhibitors may increase mortality from hemophilia by increasing bleeding-related deaths.[7]

Patients who develop inhibitors typically do so soon after exposure to factor VIII (generally before 10 or 20 doses of factor VIII are administered).[8] In some patients, inhibitors can be eradicated by inducing immune tolerance with high and then continual doses of factor VIII (immune tolerance induction [ITI]).[9,10] This report focuses on patients who will not be treated with ITI or for whom ITI has been unsuccessful.

Patients with high levels of inhibitors to factor VIII who bleed are treated with "bypassing agents" (BPAs) such as activated prothrombin complex concentrate (aPCC; FEIBA™, Shire) or recombinant activated factor VII (rFVIIa; NovoSeven®, Novo Nordisk).[10] Treatment of a single bleeding episode can cost $50,000 or more, and some patients are treated prophylactically with BPAs, which can generate very high costs (estimates range from $300,000 to $2.5 million per year).[11,12] Even with BPA prophylaxis, many patients continue to have frequent episodes of bleeding.[11,13]

Administration of Factors/BPAs

Factor VIII and the BPAs are given intravenously, whether administered on-demand or prophylactically. Prophylaxis is administered multiple times per week. Intravenous access requires skill and can be painful and difficult to master. 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 factors 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. Implanted venous access devices (ports) are frequently

required for young children; however 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 an issue for patients who are appropriate candidates for prophylaxis. Even in the absence of inhibitors, only 50%-70% of patients adhere to prophylaxis regimens, particularly once they are old enough to make treatment decisions for themselves.[14,15]

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 (see Figure 1.1 in main report).[13] Emicizumab was approved by the United States (US) Food and Drug Administration (FDA) on November 16, 2017 as a prophylactic treatment for hemophilia A in patients who have inhibitors to factor VIII.[16]

Emicizumab is administered subcutaneously and is dosed weekly, with less frequent dosing also being studied. It is also being studied as a potential alternative for prophylaxis in patients without inhibitors. Patients with inhibitors who require treatment for bleeding while receiving emicizumab will generally still need to be treated with a BPA. There have been clotting complications in some patients on emicizumab who received large amounts of the BPA aPCC as treatment for bleeding.[13] However, for patients with severe hemophilia A who have inhibitors, a more effective and easily administered prophylactic therapy could be life changing.

The wholesale acquisition cost (WAC) of emicizumab is approximately $482,000 for the first year of treatment and $448,000 for subsequent years (individual dosing and thus cost is based on weight, and therapy may be used both in young children and adults). While this cost is high, emicizumab could potentially reduce the need for other costly therapies. This report compares prophylaxis with emicizumab to (1) no prophylaxis, and (2) prophylaxis with BPAs in patients with hemophilia A with inhibitors to factor VIII who will not be treated with ITI or for whom ITI has been unsuccessful. Emicizumab was evaluated under ICER's framework for a serious ultra-rare condition (https://icer-review.org/wp-content/uploads/2017/11/ICER-Adaptations-of-Value-Framework-for-Rare-Diseases.pdf).

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 into 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, as patients who require multiple doses per week of factor VIII, rFVIIa, or aPCC 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. With ITI, some children may require more than one infusion per day. 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 child-care 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	×	×	×	

Comparative Clinical Effectiveness

We identified five references (one publication and four conference abstracts) relating to two trials of emicizumab. The first trial (HAVEN 1) was a phase III open-label study (RCT) conducted in adults and adolescent males between the ages of 12 and 75 years with hemophilia A (any severity) and a history of high titer factor VIII inhibitors.[13] HAVEN 1 included a randomized comparison between emicizumab and no prophylaxis in 53 patients who had not previously been receiving prophylaxis with BPAs, and also an observational study in an additional 49 patients who had previously been receiving BPAs (and on whom data had been collected previously) and were then all administered emicizumab. The randomized comparison between emicizumab prophylaxis and no prophylaxis was judged to be of good quality, while the comparison between emicizumab prophylaxis and prior BPA use was judged to be of fair quality.

The second emicizumab trial (HAVEN 2) is an ongoing phase III single-arm, open-label, multicenter trial clinical trial in children (<12 years or 12-17 years if < 40 kg). Interim analysis for this trial is only available in a conference abstract; therefore, a quality rating was not assigned to it. Participants in HAVEN 2 were enrolled if they had hemophilia A of any severity, a history of high titer factor VIII inhibitors, and required treatments with BPAs. At the time of the interim analysis, 60 patients (median age: 7 years, range: 1-15 years) had been enrolled and followed for a median observation of 9 weeks (range: 1.6 - 41.6).

We identified six additional published references relating to three trials assessing the efficacy of prophylaxis with BPA (two on aPCC prophylaxis and one on rFVIIa prophylaxis), and all were judged to be of fair quality.

Clinical Benefits

The randomized HAVEN 1 trial found that prophylaxis with emicizumab substantially reduced bleeding events in adolescents and adults (ages 12 years and older) compared to no prophylaxis, and also compared to prior prophylaxis with BPAs. Interim results from the single-arm HAVEN 2 trial indicated that prophylaxis with emicizumab prevented bleeding events in most children; a substantial improvement was observed with emicizumab when compared to prior prophylaxis with BPAs. Compared with no prophylaxis, emicizumab also improved health-related quality of life and caregiver burden.

Bleeding Outcomes

We did not quantitatively compare the bleeding outcomes presented in the emicizumab trials to the BPA trials due to important differences in the patient populations and in the way the bleeding outcomes were presented in the studies: adult and pediatric populations were assessed in two separate emicizumab trials, while the BPA trials included a mix of pediatric and adult patients; bleeding events were presented as annualized rates in emicizumab trials, while these were annualized in only one of the BPA trials; none of the BPA studies clearly stated if the bleeding outcomes reported were "treated bleeds" or "all bleeds" (including untreated bleeds) as described in the emicizumab trials; however, we inferred from the description of the studies that the bleeding outcomes in the three BPA trials referred to treated bleeds; detection of events (such as bleeding events) was done with a mobile app in the HAVEN trials, while the method of detection was unclear in the earlier BPA trials.

The primary outcome in the HAVEN 1 trial was the difference in the annualized bleeding rate (ABR) for "treated bleeds" between participants who received weekly emicizumab prophylaxis (group A; median follow up: 29 weeks) and those who received no prophylaxis (group B; median follow up: 24 weeks).[13] This and other bleeding outcomes are shown in Table ES2.

In the observational study, intra-individual analysis of patients with available data on prior BPA use (n=24) showed significantly lower bleeding rate on emicizumab prophylaxis at 24 and 55 weeks (see Table ES3).

Interim analyses from HAVEN 2 followed 23 patients for up to 12 weeks and reported ABRs for "treated bleeds" and "all bleeds" (treated and untreated) of 0.2 (95% CI: 0.06-0.62) and 2.9 (95% CI: 1.75-4.94), respectively (see Table ES4).[17] Observational intra-individual analysis of patients with available data on prior BPA use (n=13) showed there was a substantial lower bleeding rate after about 12 weeks on emicizumab prophylaxis when compared with previous BPA prophylaxis use (ABR: 0.2 vs. 17.2, RR=0.01; p-value not reported).[17] At interim analysis, many children in HAVEN 2 had experienced no bleeding events (see Table ES5).

Only one of the BPA trials (PROOF) presented an annualized rate of bleeding event. PROOF is a Phase III, open-label trial that randomly assigned male patients between the ages of 4 and 65 years old with hemophilia A or B of any severity and a history of a high titer of factor VIII inhibitors to either aPCC prophylaxis (every other day) or to no prophylaxis for 12 months. The median ABR was a primary outcome and was lower in patients on aPCC prophylaxis compared to no-prophylaxis (7.9 vs. 28.7; RR=0.28; p=0.0003).[18]

Table ES2. Bleeding Outcomes in the Randomized Arms of HAVEN 1

Bleeding Outcomes	Randomized Study Arms*		Emicizumab vs. No Prophylaxis	
	Emicizumab Prophylaxis (n=35)	No Prophylaxis (n=18)		
	ABR† (95% CI)		Risk Ratio	p Value
Treated Bleeds‡	2.9 (1.69, 5.02)	23.3 (12.33, 43.89)	0.13	<0.0001
All Bleeds (Treated + Untreated)	5.5 (3.58, 8.60)	28.3 (16.79, 47.76)	0.20	<0.0001
Treated Spontaneous Bleeds	1.3 (0.73, 2.19)	16.8 (9.94, 28.30)	0.08	<0.0001
Treated Joint Bleeds	0.8 (0.26, 2.20)	6.7 (1.99, 22.42)	0.11	0.0050
Treated Target Joint Bleeds	0.1 (0.03, 0.58)	3.0 (0.96, 9.13)	0.05	0.0002

ABR: annualized bleeding rate

*Other non-randomized study arms not presented

†ABR was calculated by using a negative binomial regression model to determine bleeding rate per day, which was converted to an annual rate

‡Primary outcome

Table ES3. Emicizumab Prophylaxis Versus Prior BPA Prophylaxis in HAVEN 1 Trial

Median Efficacy Period for Emicizumab	N=24		Emicizumab vs. Prior BPA	
	Emicizumab Prophylaxis	Prior BPA Prophylaxis		
	ABR For Treated Bleeds* (95% CI)		Risk Ratio	p Value
24 Weeks	3.3 (1.3, 8.1)	15.7 (11.1, 22.3)	0.21	<0.001
55 Weeks	2.1 (0.9, 5.1)		0.13	<0.0001

*ABR was calculated by using a negative binomial regression model to determine bleeding rate per day, which was then converted to an annual rate

Table ES4. Bleeding Outcomes in HAVEN 2 Trial

	ABR (95% CI)	Number of Patients with Zero Bleeds (%)
Number of Patients Included in Analysis	23	57
Types of Bleed		
Treated Bleeds*	0.2 (0.06, 0.62)	54 (94.7)
All Bleeds (Treated + Untreated)	2.9 (1.75, 4.94)	37 (64.9)
Treated Spontaneous Bleeds	0.1 (0.01, 0.47)	56 (98.2)
Treated Joint Bleeds	0.1 (0.01, 0.47)	56 (98.2)
Treated Target Joint Bleeds	--	57 (100)

*Primary outcome

Table ES5. Emicizumab Prophylaxis Versus Prior BPA Prophylaxis in HAVEN 2 Trial

ABR on Emicizumab Prophylaxis (95% CI)	ABR on Prior BPA Prophylaxis (95% CI)	Risk Ratio	p Value
0.2 (0.1, 0.8)	17.2 (12.4, 23.8)	0.01	NR

Health-Related Quality of Life and Other Outcomes

Emicizumab prophylaxis improved health-related quality of life as measured by Haem-A-QoL and EQ-5D-5L when compared to no prophylaxis (HAVEN 1) or to baseline (HAVEN 2); and improvement from baseline in caregiver burden as measured by inhib-QOL in HAVEN 1. Emicizumab appeared to improve attendance at day care, school or work, and to reduce hospitalized days, although statistical significance for these outcomes was not reported. Prophylaxis with BPAs did not result in statistically significant improvement in health-related quality of life as measured by EQ-5D in the three included trials.

We did not identify any studies that assessed the impact of prophylaxis with emicizumab or BPAs on joint outcomes or mortality.

Harms

An increased risk of thrombotic microangiopathy and thrombotic events were observed in patients on emicizumab who received large and multiple doses of aPCC for treatment of bleeding events.

The most common treatment-related adverse event (AE) in both HAVEN 1 and 2 was injection site reaction, occurring in 15% to 17% of patients on emicizumab prophylaxis.[13,17] Most were mild in intensity.

Serious AEs occurred in 9% to 11% of patients on emicizumab prophylaxis, and included thrombotic microangiopathy in three patients, cavernous sinus thrombosis in one patient, and skin necrosis (and superficial thrombophlebitis) in one patient. All thrombotic microangiopathy and thrombotic events occurred in HAVEN 1 and were in patients who had received multiple doses of aPCC for bleeding (averaging more than 100 U/kg) while on emicizumab prophylaxis.[13] The two cases of thrombotic microangiopathy resolved following discontinuation of aPCC without requiring anticoagulation. There were was no thrombotic microangiopathy or thromboembolic events, or any serious adverse events (SAEs) deemed to be treatment related in preliminary reports from HAVEN 2.[17]

In the aPCC trials, poor venous access (3%), catheter-site hemorrhage (6%), and catheter-site infection (9%) were the most common treatment-related AEs.[11] There were no reports of thrombotic microangiopathy or thromboembolism in any of the BPA prophylaxis trials included in this review. However, thromboembolic events have been observed in other trials and safety surveillance studies.[19,20] The FDA placed a boxed warning for thrombotic microangiopathy and thromboembolism in the label for emicizumab, noting that benefits and risks must be considered before using aPCC in patients receiving emicizumab.[21]

Controversies and Uncertainties

Emicizumab is a new therapy with a novel mechanism of action. We lack long-term safety data, and it is possible that so-far undetected toxicities and adverse events will be encountered over time,[22] or that the rates of thrombotic microangiopathy and thrombotic events will be higher than seen in the clinical trials. As a novel therapy for an ultra-rare disorder, it is not surprising that we lack such evidence for emicizumab.

We have only observational data comparing emicizumab prophylaxis with BPA prophylaxis; the intra-study data compare emicizumab when it was administered as part of a clinical trial to BPA prophylaxis measured before the intervention period began.[13,17] As such, patients may have been more adherent to therapy during the interventional time period, which would tend to make emicizumab appear more effective than BPAs.

While we modeled a decrease in joint damage with reduced bleeding, we assumed no reduction in mortality, given the lack of data. If reductions in bleeding with prophylaxis correlate with reduction in mortality, the relative benefit with emicizumab will be larger than estimated in our modeling.

The safety of emicizumab has not been evaluated in many clinical settings that could affect coagulation or the need for coagulation. These include sepsis, head trauma, major trauma, and the presence of central lines.

Summary and Comment

Methodologic limitations in trials of emicizumab include relatively short follow-up and the lack of head-to-head randomized comparisons with BPAs. Given that this patient population is small enough to qualify as ultra-rare, a head-to-head study versus a BPA would not be expected for regulatory approval. Despite these limitations, we find that:

- In adults, prophylaxis with emicizumab is efficacious in reducing bleeding events compared with no prophylaxis and improves quality of life. Observational data collected in the HAVEN 1 trial suggest that emicizumab is more effective in reducing bleeding events than prophylaxis with BPAs (aPCC and rFVIIa).
- In children, observational data collected in the HAVEN 2 trial suggest that emicizumab is more effective in reducing bleeding events than prophylaxis with BPAs. BPA prophylaxis reduces bleeding events compared with no prophylaxis, so we conclude that emicizumab also reduced bleeding events compared with no prophylaxis.
- Long-term outcomes were not measured in the trials of emicizumab. It is possible that reducing bleeding events will also reduce joint damage and lower mortality.
- The safety of any new therapy is an important consideration, and a small number of patients experienced thrombotic microangiopathy and thrombotic events with emicizumab. While there is a suggestion that these may only occur when patients are also treated with high doses of aPCC, there is still relatively little experience with emicizumab prophylaxis. The safety of emicizumab in patients experiencing events that can alter coagulation or the need for coagulation, such as sepsis or major trauma, has not been assessed. We also have more limited evidence on safety in patients younger than age 12 than in older patients.
- Although not directly reported in trials, emicizumab is substantially less burdensome for patients and families than BPAs. Emicizumab is administered by subcutaneous injection once per week, while BPAs are administered by intravenous infusion multiple times per week.

In summary, for people ages 12 and older with hemophilia A with inhibitors who will not be treated with ITI or for whom ITI has been unsuccessful, we have high certainty that emicizumab provides a substantial net health benefit ("A") compared with no prophylaxis. This reflects our belief that the large reductions in bleeding events exceed possible harms from thrombotic microangiopathy and thrombotic events. Given limitations in evidence on the safety of emicizumab, as well as only observational data comparing emicizumab with BPAs in all patients, and comparing emicizumab with no prophylaxis in children, our certainty of the net health benefit for these comparisons is somewhat smaller. Despite this, given the results of the trials and the reduced burden with emicizumab, for children younger than 12 we have high certainty that emicizumab provides at least a small net health benefit ("B+") compared with no prophylaxis, and in adults and children we have

high certainty that emicizumab provides at least a small health benefit ("B+") compared with prophylaxis with BPAs.

Long-Term Cost Effectiveness

We conducted a cost-effectiveness analysis using a *de novo* Markov model comparing emicizumab prophylaxis to two alternative strategies in male hemophilia A patients with inhibitors to factor VIII who will not be treated with ITI or for whom ITI has been unsuccessful: 1) BPA prophylaxis and 2) no prophylaxis. Consistent with the patient populations treated with emicizumab in HAVEN 1 and 2[13,17], our target populations were in two age categories, 12 years and older (median age of 37 years), and under 12 years of age (median age of 8.5 years). The Markov model included health states for individual bleed events as well as the development of joint arthropathy over time, with fewer joint bleeds over a lifetime leading to reduced levels of joint arthropathy. The model was run with weekly cycle lengths over a lifetime time horizon. The model was developed with dual base cases (a health system payer perspective and a societal perspective) under ICER's ultra-rare disease framework, with costs and outcomes discounted at 3% annually. A comprehensive list of choices and assumptions made in the model, along with the rationale for each, is available in section 4 of the report.

Weekly transition probabilities were derived from HAVEN 1 and 2 trial data for emicizumab and from the PROOF trial for BPAs.[13,17,18] Increases in the Pettersson score (a validated radiological scoring system that assesses the sum of joint damage in a patient) drove new arthropathy development and joint replacement surgery.[23] We applied a 70% increase in odds of mortality to the background mortality in this target population, based on retrospective data on mortality in hemophilia A patients with inhibitors;[7] this was applied equivalently to all three strategies due to a lack of treatment-specific long-term survival data. Utility values for health states were consistent across treatments evaluated in the model (Table ES6).

Table ES6. Utility Values for Health States

Parameter	Value
Utility: Hemophilia A With Inhibitors, No Bleed[24]	0.82
Utility: Hemophilia A With Inhibitors, Treated Bleed Not Into A Target Joint[24]	0.66
Utility: Hemophilia A With Inhibitors, Target Joint Bleed*[25]	0.54
Utility: No Bleed With Arthropathy, By Pettersson Score (PS)[26]	
• PS 0-4	0.82
• PS 4-12	0.81
• PS 13-21	0.77
• PS 22-39	0.74
• PS 40-78	0.72
Disutility: Orthopedic Surgery[27]	-0.39

*Calculated as utility of "hemophilia A patients with inhibitors, treated bleed not into a target joint" (0.66) minus disutility of "hemophilia A with inhibitors, target joint bleed" (-0.12)

All costs were reported in 2017 US dollars and inflated as necessary to these values. All therapies were weight-based regimens (Table 4.4), with appropriate age-based weights derived from the Centers for Disease Control and Prevention (CDC) data.[28] The cost of on-demand BPA therapy for a single bleeding event, which was based on a weighted average of units/kg (for both rFVIIa and aPCC) in arms A and B of HAVEN 1, was equivalent across all three comparators, at $50,589 for a 75kg patient. For prophylaxis, we used the average sales price (ASP) for the BPA comparators, as an estimate of price net of discounts, rebates, and other concessions was not available (Table ES7).[29] For emicizumab, we used the WAC because we did not identify any sources on potential discounts from WAC; we acknowledge that using an undiscounted price disadvantages emicizumab from a cost perspective in the model (Table 4.6).[30] The model included health care utilization costs associated with physician office visits for education on treatment self-administration, hospitalizations for bleed events, arthropathy-related joint surgery, and visits to hemophilia treatment centers. To estimate these costs, we used recently published claims data from a large, geographically diverse patient population, representing a broad age range in its database [31]; and inputs from a previously published model.[32] Treatment-specific adverse events and associated costs, and other supportive care costs, were also included in the model. Adverse event rates were based on the HAVEN 1 trial data [13], and unit prices for their associated treatments were taken from the Centers for Medicare and Medicaid Services (CMS) Medicare Physician Fee Schedule for fiscal year 2017.[33] Detailed explanations of model inputs are presented in section 4 of the report.

Model outputs include quality-adjusted life years (QALY) gained, life years (LYs), number of bleed events, and total costs for intervention and comparators, as well as incremental costs per additional QALY gained and per additional LY gained for the intervention relative to the comparators. In additional to the dual-base case analysis (that includes the health system and modified societal

perspective), sensitivity and scenario analyses were conducted, with detailed descriptions of these additional analyses presented in section 4 of the report.

Base-Case Results

In both patient populations, emicizumab resulted in fewer total bleed events, higher QALYs, and lower total costs relative to no prophylaxis and to prophylaxis with BPAs over a lifetime time horizon from both the health system and societal perspectives (Table ES7 – ES10). Total life years were equivalent among strategies since we did not model overall survival differences due to a lack of treatment-specific long-term survival data. These results were robust to parameter variation in multiple sensitivity and scenario analyses.

Table ES7. Health System Perspective Results for Emicizumab Prophylaxis Compared to BPA Prophylaxis and No Prophylaxis

Treatment	Prophylaxis Drug Cost	Cost of On-Demand Treated Bleeds	Total Cost	Total Bleed Events (All)	Life Years	QALYs
Patients ≥ 12 Years of Age						
Emicizumab Prophylaxis	$14,952,461	$3,817,130	$19,221,932	107	21.28	15.41
BPA Prophylaxis	$81,418,150	$7,907,405	$90,182,398	221	21.28	15.21
No Prophylaxis	--	$25,525,761	$28,135,154	713	21.28	14.50
Patients < 12 Years of Age						
Emicizumab Prophylaxis	$16,461,362	$3,904,537	$20,683,787	176	28.06	22.79
BPA Prophylaxis	$89,865,693	$8,731,838	$99,212,053	392	28.06	22.41
No Prophylaxis	--	$28,187,098	$31,012,935	1267	28.06	20.40

BPA: bypassing agent, QALY: quality-adjusted life year

Table ES8. Health System Perspective Incremental Results

Treatment	Incremental Cost	Incremental Bleeds Avoided	Incremental QALYs Gained	Incremental Life Years Gained
Patients ≥ 12 Years of Age				
Emicizumab vs. No Prophylaxis	-$8,913,222	606	0.91	0
Emicizumab vs. BPA	-$70,960,466	114	0.20	0
Incremental C-E Ratio	--	**Less Costly, More Effective**	**Less Costly, More Effective**	**Less Costly, Equally Effective**
Patients < 12 Years of Age				
Emicizumab vs. No Prophylaxis	-$10,000,971	1091	2.39	0
Emicizumab vs. BPA	-$78,528,265	217	0.38	0
Incremental C-E Ratio	--	**Less Costly, More Effective**	**Less Costly, More Effective**	**Less Costly, Equally Effective**

BPA: bypassing agent, C-E: cost-effectiveness, QALY: quality-adjusted life year

Table ES9. Societal Perspective Results for Emicizumab Prophylaxis Compared to BPA Prophylaxis and No Prophylaxis

Treatment	Indirect Cost	Total Cost
Patients ≥ 12 Years of Age		
Emicizumab Prophylaxis	$400,983	$19,623,275
BPA Prophylaxis	$400,983	$90,583,742
No Prophylaxis	$766,602	$28,901,756
Patients < 12 Years of Age		
Emicizumab Prophylaxis	$528,743	$21,212,892
BPA Prophylaxis	$528,743	$99,741,157
No Prophylaxis	$1,010,856	$31,695,614

BPA: bypassing agent

Table ES10. Societal Perspective Incremental Results

Treatment	Incremental Indirect Cost	Incremental Total Cost
Patients ≥ 12 Years of Age		
Emicizumab vs. No Prophylaxis	-$365,619	-$9,278,481
Emicizumab vs. BPA	$0	-$70,960,466
Incremental C-E Ratio	--	**Less Costly, More Effective**
Patients < 12 Years of Age		
Emicizumab vs. No Prophylaxis	-$482,112	-$10,482,722
Emicizumab vs. BPA	$0	-$78,528,265
Incremental C-E Ratio	--	**Less Costly, More Effective**

BPA: bypassing agent, C-E: cost-effectiveness, QALY: quality-adjusted life year,

*The incremental total costs in the health system and societal perspective are identical because the same societal cost associated with prophylaxis for emicizumab was assumed as reported for BPA prophylaxis; hence these cancel each other out.

Sensitivity and Scenario Analysis Results

All input parameters were subjected to sensitivity analyses. The result that emicizumab is cost saving was robust to changes in all input parameters. The incremental QALY gain for emicizumab remained until the utility of "No Bleed" was lowered to a value of 0.66.

Multiple scenario analyses were conducted to evaluate the impact of key model choices and assumptions on the robustness of the results and conclusions, including:

- Varying age at model entry;
- Reduced mortality resulting from lower ABR;
- Higher bleed rates in patients with arthropathy;
- Proportion of patients able to use aPCC on demand when treated with emicizumab;
- Bleeding reduction persisting at the childhood (i.e., < 12 years) level beyond the age of 12 years; and
- A "BPA-favoring scenario" analysis (available in Appendix Tables F8-F9), where we made multiple assumptions disadvantaging emicizumab prophylaxis compared to BPA prophylaxis.

In all scenarios, emicizumab remained cost saving and had more QALYs gained compared to no prophylaxis and prophylaxis with BPAs.

Threshold Analyses

The WAC price per unit (1.5 mg) of emicizumab is $148.80. The unit price at which it would no longer be cost saving is approximately $238 when compared to no prophylaxis and approximately $856 when compared to BPA prophylaxis. Unit prices for cost-effectiveness at thresholds ranging

from $50,000 to $500,000 per QALY gained are in a narrow range and similar to the prices at which it ceases to be cost saving (see Table 4.15 and Table 4.16); there is substantial volatility in the incremental overall costs with small changes in the unit price of emicizumab. Threshold costs presented in this report are specific to the inhibitor population only.

Summary and Comment

Our analysis indicates that in hemophilia patients with inhibitors to factor VIII who will not be treated with ITI or for whom ITI has been unsuccessful, emicizumab prophylaxis compared to no prophylaxis or to prophylaxis with BPAs would be cost-saving. Emicizumab was estimated to be more effective and to generate more QALYs at lower total cost, both from a health system and societal perspective, compared to no prophylaxis and to prophylaxis with BPAs.

Additional Considerations

Our reviews seek to provide information on 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. These elements are listed in the table below. As emicizumab was evaluated under ICER's framework for a serious ultra-rare condition (https://icer-review.org/wp-content/uploads/2017/11/ICER-Adaptations-of-Value-Framework-for-Rare-Diseases.pdf) additional elements appear in the table that are assessed for such conditions.

Other Benefits

Table ES11. Potential Other Benefits

Other Benefits	Description
This intervention provides significant direct patient health benefits that are not adequately captured by the QALY.	Having a more effective therapy should enhance career and education choices.
This intervention offers reduced complexity that will significantly improve patient outcomes.	Weekly subcutaneous therapy is less burdensome and has reduced complexity, which is likely to improve adherence as well as the ability for some patients with limited mobility to self-administer prophylaxis; intravenous administration has been identified as a barrier to starting and adhering to prophylaxis.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.	N/A
This intervention will significantly reduce caregiver or broader family burden.	Caregivers will find administering therapy much less burdensome and time consuming, and, in young children, will not need to deal with techniques required to reduce the risks of infection and thrombosis in central venous access devices (ports).
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients who have failed other available treatments.	Emicizumab offers a novel mechanism of action, and so is likely to benefit patients who did not achieve adequate prophylaxis with BPAs.
This intervention will have a significant impact on improving return to work and/or overall productivity.	Having a more effective therapy should enhance career and education choices which may in turn affect productivity.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.	N/A
This intervention will have a significant positive impact outside the family, including on schools and/or communities.	Having a more effective therapy should reduce burdens on schools and communities by potentially allowing children to participate in activities from which they would previously have been restricted.
This intervention will have a significant impact on the entire “infrastructure” of care, including effects on screening for affected patients, on the sensitization of clinicians, and on the dissemination of understanding about the condition, that may revolutionize how patients are cared for in many ways that extend beyond the treatment itself.	N/A

Contextual Considerations

Table ES12. Potential Contextual Considerations

Contextual Consideration	Description
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.	Hemophilia creates substantial burdens that affect quality of life and can also affect length of life.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	Hemophilia is a disease that affects patients for their entire lives.
This intervention is the first to offer any improvement for patients with this condition.	N/A
Compared to prophylaxis with BPAs, there is significant uncertainty about the long-term risk of serious side effects of this intervention.	There are important uncertainties about the risks of thrombosis in patients treated with emicizumab, particularly when situations occur that might alter coagulation or the need for coagulation, such as sepsis, head trauma, major trauma, and central lines.
Compared to prophylaxis with BPAs, there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.	N/A
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.	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.

Potential Budget Impact

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential cost of using the new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. We estimated the eligible prevalent population, derived from published reports and literature, at 634 patients ≥12 years and 327 patients under 12 years old respectively.[34-36]

The per-patient annual budget impact of emicizumab at its WAC relative to a 50:50 mix of prophylaxis with BPAs and no prophylaxis is a savings of approximately $1.85 million and approximately $720,000 in the populations ≥12 years and <12 years old, respectively (Table ES13). This translates into annual savings of approximately $706 million and $146 million in the entire eligible populations ≥12 years and <12 years old, respectively.

Table ES13. Per-Patient Budget Impact Calculations Over a Five-year Time Horizon for Eligible Patient Populations, using Emicizumab WAC

	Average Annual Per Patient Budget Impact	
	≥ 12 years old	< 12 years old
Emicizumab Prophylaxis	$974,560	$265,618
Prophylaxis with BPA + No Prophylaxis*	$2,827,256	$985,416
Difference	-$1,852,696[†]	-$719,798[†]

*In a 50:50 ratio

[†]Cost-saving

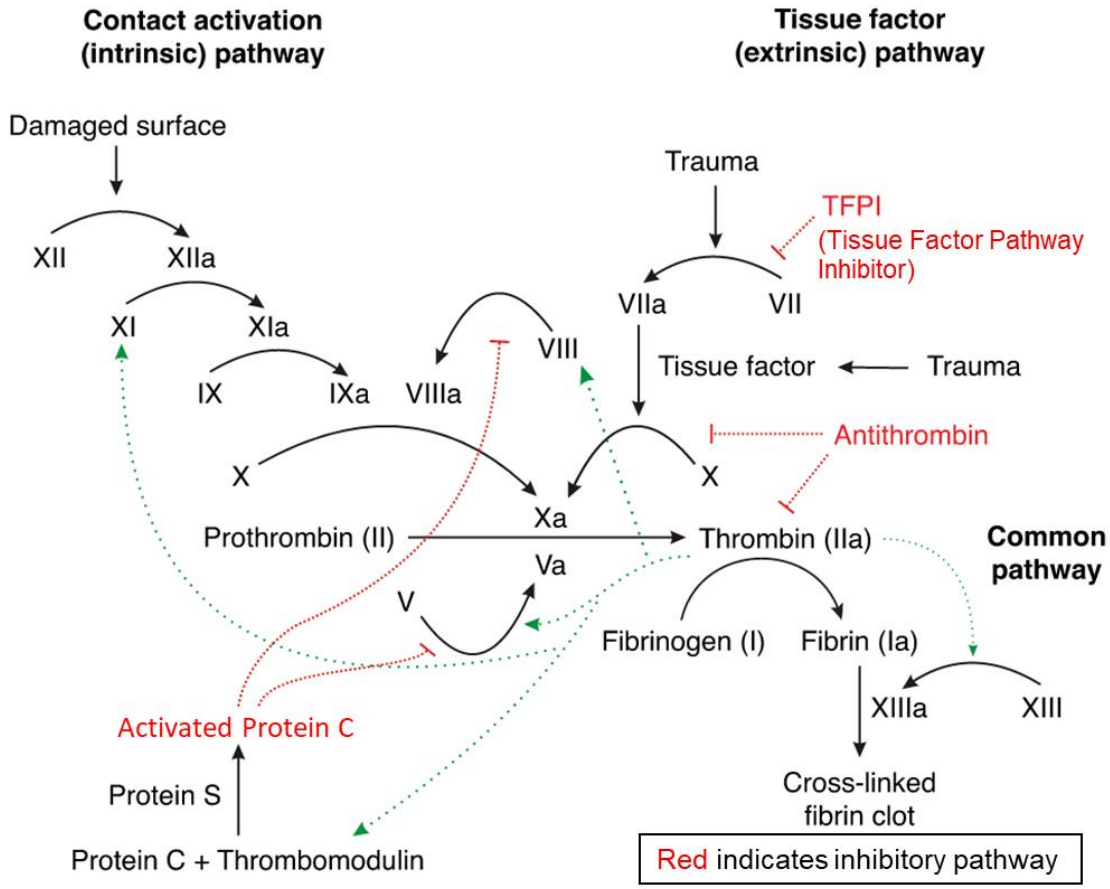
1. Introduction

1.1 Background

Hemophilia A

Hemophilia A is a condition of increased tendency to bleed due to an inherited deficiency of factor VIII, which disrupts the clotting cascade (Figure 1.1). 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]

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.

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).[37] However, severity based on factor levels does not perfectly correlate with actual clinical severity.[38] 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.[37] 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 5% 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 typically administer 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.

Hemophilia

From ancient times through the 1800s, hemophilia was described by its symptoms and defined by those descriptions. From the 1840s through the 1940s, bleeding in hemophilia was treated with blood transfusions.[39] In the 1930s, deficiency in factor VIII (originally called "anti-hemophilic globulin") was identified as a cause of hemophilia (factor IX deficiency, the etiology of hemophilia B, was first elucidated in the 1950s).[39] In the 1950s, an impure fraction of plasma containing factor VIII was administered intravenously as a treatment for bleeding in hemophilia A, and was first used for prophylaxis.[39,40] The supply of factor VIII was very limited, but in the 1960s, cryoprecipitate, rich in factor VIII, was developed.[39,41] In the 1970s, factor VIII and factor IX concentrates that could be reconstituted with small amounts of liquid and injected became available, which permitted home treatment of hemophilia A and hemophilia B, respectively.[41] The availability of these concentrates allowed prophylaxis to become more common and also allowed patients with hemophilia A and B to safely undergo invasive procedures.[41] Bypassing agents (activated prothrombin complex concentrates and recombinant activated factor VII) became available in the 1970s and 1990s, respectively, for the treatment of patients with inhibitors to factor VIII (discussed further below).[42,43] In the 2000s, randomized trials demonstrated the superiority of prophylaxis over on-demand treatment for hemophilia, first for patients without inhibitors and later for those with inhibitors.[18,44]

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.[41] 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.

Factor Inhibitors

Approximately one-quarter of patients with severe hemophilia A who receive factor VIII concentrates develop neutralizing antibodies known as "inhibitors."[5] Inhibitors neutralize infused factor VIII, rendering it ineffective for prophylaxis (i.e., prevention) and on-demand treatment. Inhibitors may be diagnosed as part of routine laboratory testing in people with hemophilia, or when testing is performed because of inadequate response to factor VIII that is administered to control bleeding.[10] As discussed below, inhibitors can resolve with treatment.[10] The overall prevalence of inhibitors across severity levels is approximately 5% to 7%.[8] The prevalence of hemophilia A in the United States is estimated to be around 15,500,[34,45] which suggests a total population of patients with inhibitors of around 950.[6] Patients who develop inhibitors typically do so soon after exposure to factor VIII (generally before 10 or 20 doses of factor VIII are administered).[8] The presence of inhibitors may increase mortality from hemophilia by increasing bleeding-related deaths.[7]

Patients with low levels of inhibitors who bleed can often be treated with higher doses of factor VIII, while those with high levels of inhibitors are treated with "bypassing agents" (BPAs) such as activated prothrombin complex concentrate (aPCC; FEIBA™, Shire) or recombinant activated factor VII (rFVIIa; NovoSeven®, Novo Nordisk).[10] Treatment of a single bleeding episode can cost $50,000 or more, and some patients are treated prophylactically with BPAs, which can generate very high costs (estimates range from $300,000 to $2.5 million per year).[11,12] Even with BPA prophylaxis, many patients continue to have frequent episodes of bleeding.[11,13]

In some patients, inhibitors can be eradicated by inducing immune tolerance with high and then continual doses of factor VIII, which is also expensive but allows for prophylactic and on-demand therapy with factor VIII alone when successful.[9] Immune tolerance induction (ITI) regimens sometimes include the use of immune modulators such as rituximab.[10] ITI is successful in about three-fourths of patients with inhibitors.[9]

Administration of Factors/BPAs

Factor VIII and the BPAs are given intravenously, whether administered on-demand, prophylactically, or for ITI. Prophylaxis is administered multiple times per week, and ITI may require daily administration of factor VIII.

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 factors 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, particularly if ITI is involved. 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 an issue for patients who are appropriate candidates for prophylaxis. Even in the absence of inhibitors, only 50%-70% of patients adhere to prophylaxis regimens, particularly once they are old enough to make treatment decisions for themselves.[14,15]

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 1.1).[13] Emicizumab was approved by the United States (US) Food and Drug Administration (FDA) on November 16, 2017 as a prophylactic treatment for hemophilia A in patients who have inhibitors to factor VIII.[16]

Emicizumab is administered subcutaneously, and is dosed weekly, and is also being studied as a potential alternative for prophylaxis in patients without inhibitors. Less frequent dosing is also being studied. Patients with inhibitors who require treatment for bleeding while receiving emicizumab will generally need to be treated with a BPA. There have been clotting complications in some patients on emicizumab who received large amounts of the BPA aPCC as treatment for bleeding.[13] However, for patients with severe hemophilia A who have inhibitors, a more effective and easily administered prophylactic therapy could be life changing.

The wholesale acquisition cost (WAC) of emicizumab is approximately $482,000 for the first year of treatment and $448,000 for subsequent years (individual dosing and thus cost is based on weight,

and therapy may be used both in young children and adults), but it could potentially reduce the need for other costly therapies.

Expanded Use of Emicizumab in Patients with Inhibitors

As discussed above, ITI is typically attempted when patients first develop factor VIII inhibitors, which occurs very early in the course of therapy with factor VIII,[8] most often in young children after 9-10 doses of factor VIII. ITI can take weeks or up to a year, and sometimes longer. About three-fourths of patients treated with ITI clear their inhibitors and can receive routine prophylaxis and treatment with factor VIII,[9] while in about one-fourth of patients ITI does not succeed. However, this distinction is not always clear cut. Some patients remain on ITI with intermediate levels of inhibitors and appear to both get some benefit in terms of reductions in bleeding and may have some ability to respond to additional factor VIII when they bleed.

Although the scope of our review (see Section 1.2) is limited to patients who will not be treated with ITI or for whom ITI has been unsuccessful, there are a number of potential applications of emicizumab in patients who are candidates for ITI or are on ITI. In the absence of trial data, we heard starkly differing views from experts on the appropriateness of emicizumab in these settings. It is clear, however, that over time some clinicians are likely to try using emicizumab in patients for whom ITI has not yet failed and that with clinical experience there is likely to be greater consensus on appropriate use.

Specific situations/issues include:

- When patients first develop inhibitors (typically as young children), ITI offers the possibility of returning to use of factor VIII as in patients without inhibitors. Some clinicians felt strongly that all patients should have a chance at this option. Other clinicians felt that emicizumab could obviate the need for ITI. Inhibitor levels would be expected to decrease over time in the absence of treatment with factor VIII, and factor VIII might then be used acutely in a patient who was bleeding or needs surgery during the period before inhibitor levels rebound.
- Since ITI is burdensome, particularly in young children, some experts suggested that emicizumab could be used to delay the start of ITI until the patient was older.
- Some patients who are receiving ITI continue to have frequent bleeding while ITI is being attempted. Currently, these patients may receive prophylaxis with BPAs, but emicizumab could potentially be used for prophylaxis during ITI.
- Emicizumab might lead to decisions to shorten the duration of trials of ITI and to replace ITI that is neither clearly succeeding nor failing.

Expanded Use of Emicizumab in Patients without Inhibitors

In patients without inhibitors to factor VIII, emicizumab has two main potential advantages as treatment. First, it is a subcutaneous injection that can be administered once weekly rather than an intravenous infusion administered multiple times per week (like factor VIII). Second, its level of activity appears to be more constant than the varying activity seen as concentrations of factor VIII increase after an infusion and decrease prior to the next infusion.

However, emicizumab is not an exact replacement for factor VIII. It is constantly acting on factor X and factor IXa, without the ability to have its activity directly downregulated or upregulated (i.e., emicizumab is always "on").[46] Clinical trials, which are underway,[47] will be needed to assess the relative efficacy of emicizumab in this setting. However, trials simply comparing emicizumab with placebo are unlikely to provide clear answers on the relative efficacy and safety of prophylaxis with factor VIII or emicizumab.

In addition, there are potential alternatives to this use of emicizumab. Higher doses of factor VIII, or of factor VIII modified to have a longer half-life,[48] could lead to less frequent infusions while maintaining protective levels of factor VIII activity. Additionally, potentially-curative gene therapy is being evaluated in clinical trials for hemophilia A (see below). While, at present, gene therapy is not possible for patients who already have inhibitors to factor VIII, it could potentially be an attractive option for patients without inhibitors.

Future Therapies

- Fitusiran is an investigational RNA interference (RNAi) agent that targets antithrombin, is administered subcutaneously, and potentially could be used to treat hemophilia A and B in patients with or without factor inhibitors.[15] In September 2017, studies of fitusiran were placed on hold after a patient experienced a fatal thrombotic event while receiving fitusiran.[49] The hold was subsequently lifted with a plan for new risk mitigation measures.[50] Among these are avoiding high-doses or repeat doses of either factor VIII or BPA in a 24-hour period, as this may lead to thrombosis in those already receiving fitusiran.
- A number of gene therapies are being developed and under investigation to treat both hemophilia A and hemophilia B.[51-53] The rate of development of factor inhibitors with gene therapy and the safety and efficacy of gene therapy in patients who already have factor inhibitors is uncertain.[54] However, to date, there have been no inhibitors seen following gene therapy for hemophilia B or hemophilia A, however experience is more limited in hemophilia A.[55]

1.2 Scope of the Assessment

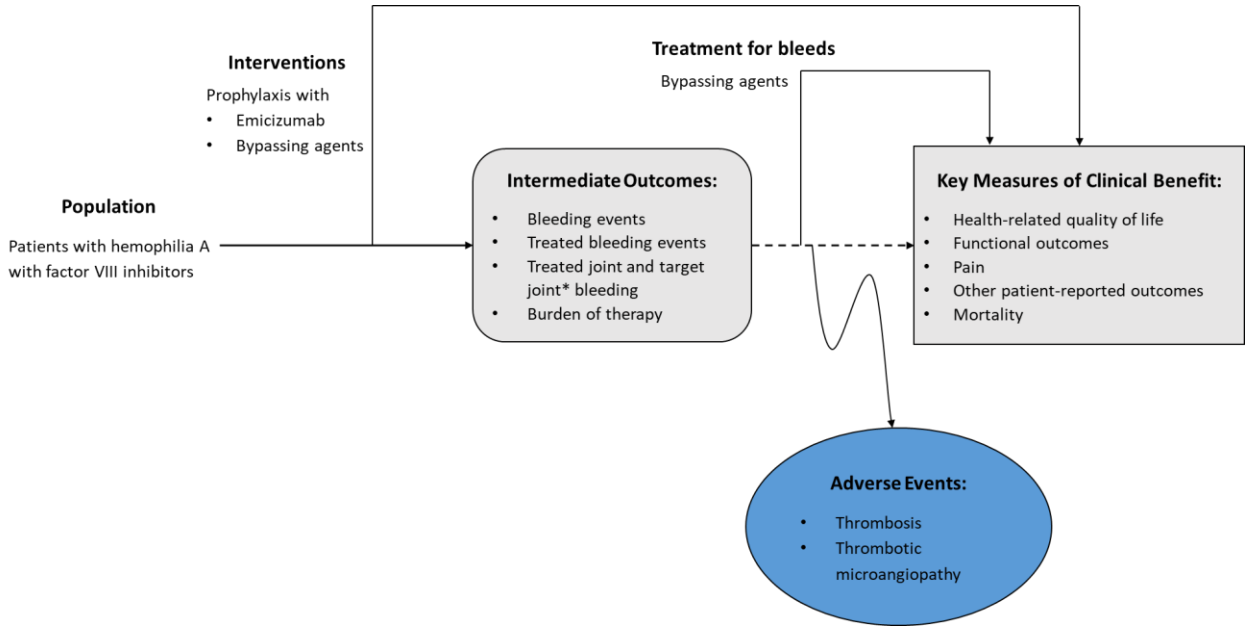
The scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence was collected from available randomized controlled trials. Observational studies and case series were considered for inclusion as well, given the limited evidence base for emicizumab and the BPAs.

Our evidence review included input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Analytic Framework

The analytic framework for this assessment is depicted in Figure 1.2.

Figure 1.2. Analytic Framework



* A target joint may be defined as a joint that had three or more bleeds in the 24 weeks before the intervention period, however the definition has changed over time and will vary across studies

The diagram begins with the population of interest on the left. Actions, such as treatment, are depicted with solid arrows which link the population to outcomes. For example, a treatment may be associated with specific health outcomes. Outcomes are listed in the shaded boxes: those within the rounded boxes are intermediate outcomes (e.g., bleeding events), and those within the squared-off boxes are key measures of benefit (e.g., health-related quality of life). The key

measures of benefit are linked to intermediate outcomes via a dashed line, as the relationship between these two types of outcomes may not always be validated. Curved arrows lead to the adverse events of treatment which are listed within the blue ellipsis.[56]

Populations

The population of focus for this review included patients with hemophilia A with inhibitors to factor VIII who will not be treated with ITI or for whom ITI was unsuccessful. We evaluated the following two subgroups by age:

- Adolescents and adults (ages 12 and older)
- Children (under 12 years)

Interventions

The intervention of interest was subcutaneous injection of emicizumab for prophylaxis. Patients could be treated with BPAs (rFVIIa or aPCC) when they bleed.

Comparators

We compared prophylaxis with emicizumab to two alternatives:

- No prophylactic therapy
- Prophylaxis with a BPA

For each comparator, patients could be treated with BPAs when they bleed.

Outcomes

Outcomes of interest from clinical trials included:

- Rates of bleeding events
- Rates of treated bleeding events
- Rates of treated joint bleeding and treated target joint bleeding
- Pain
- Mortality
- Patient-reported quality of life
- Harms
- Burdens of therapy

We looked for evidence on hospitalizations, red cell transfusion requirements, opioid dependence, and 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, as long as they met the study design criteria set forth above and measured the outcomes of interest.

Settings

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

Potential Major Advance for a Serious Ultra-Rare Condition

ICER began its review of emicizumab using changes to its value assessment framework that had been proposed for certain ultra-rare conditions. Final modifications have since been published (https://icer-review.org/wp-content/uploads/2017/11/ICER-Adaptations-of-Value-Framework-for-Rare-Diseases.pdf). The final criteria are to use this modified approach when:

- An eligible population for the treatment indication(s) including in the scope of the ICER review is estimated at fewer than approximately 10,000 individuals.
- There are no ongoing or planned clinical trials of the treatment for a patient population greater than approximately 10,000 individuals.

While the population of hemophilia A patients in the US with inhibitors is likely much less than 10,000,[8] emicizumab is being evaluated in clinical trials in patients with hemophilia A who do not have inhibitors.[47] This population is likely larger than 10,000 individuals.[1] However, since we initiated the review of emicizumab as a treatment for an ultra-rare condition, we have decided to continue its assessment under the modified framework while acknowledging the potential growth in the size of the candidate population for treatment.

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.[37]

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.[57]

Inhibitor Titer: Levels of inhibitors to factor VIII are measured in Bethesda units (BU). Patients with a plasma titer of 5 BU or more are generally described as having *high titer inhibitors*, while those with an inhibitor titer below 5 BU are generally described as having *low titer inhibitors*.

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.[58]

EuroQol Five-Dimension Scale (EQ-5D): A self-administered questionnaire that measures generic health status in a wide range of health conditions and treatments. The original version measures five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), each on a three-level scale (no problem, some problems, and extreme problems). The EQ-5D-5L expands the normal range of responses from three to five levels (no problem, slight problems, moderate problems, severe problems, and extreme problems).[59]

1.4 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 1.1). 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 into 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, as patients who require multiple doses per week of factor VIII, rFVIIa, or aPCC 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. With ITI, some children may require more than one infusion per day. 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 child care 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 1.1. 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	×	×	×	

Patients and patient groups further directed us to a review that identified patient-important outcomes that included mortality, joint damage, quality of life, number of emergency department visits and number of inpatient days, patient knowledge, adherence, missed days of school or work, and educational attainment.[60] Adherence is a critically-important issue as, even in patients who can receive prophylaxis with factor VIII, adherence is only about 50-70%.[14,15] The review suggested that rate of bleeding events is a less-useful outcome, as it acts as a surrogate for more significant patient-centric outcomes.[60]

1.5 Potential Cost-Saving Measures in Hemophilia

As described in its Final Value Assessment Framework for 2017-2019, ICER will now include in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/final-vaf-2017-2019/). ICER encourages

all stakeholders to suggest services (including treatments and mechanisms of care) currently used for people with hemophilia that could be reduced, eliminated, or made more efficient.

In responses to the draft scoping document, stakeholders focused on potential ways in which emicizumab could offset costs by reducing the use of some healthcare services (e.g., home health visits, in-home nursing support, placement of ports) and reduce the need for on-demand treatment (from fewer bleeds) and therapy for joint pain/damage. These potential changes in healthcare resources were captured in ICER's economic models and were not the intended focus of our request. Instead, we are looking for information on low-value services used in the management of hemophilia beyond the potential offsets that arise from a new intervention. We did not receive additional suggestions in response to the final scoping document but continue to seek such input.

2. Summary of Coverage Policies and Clinical Guidelines

2.1 Coverage Policies

We analyzed insurance coverage for treatment options for patients with hemophilia A who have inhibitors to Factor VIII in six New England state Medicaid programs, and 13 silver-tiered insurance plans on individual marketplaces across New England. We also spoke with stakeholders and evaluated patient survey data to understand coverage policies and affordability of care from a patient perspective.

In nearly all major New England commercial formularies, both aPCC and rFVIIa were covered as a medical benefit, requiring prior authorization and a specialty pharmacy networks for distribution. Patient advocates have acknowledged that BPAs are largely covered for patients with inhibitors, and a self-reported patient survey released by Project CALLS at the Hemophilia Federation of America in June 2017 found that patients with inhibitors were not commonly denied coverage for drug therapy.[61] While BPAs are commonly covered as a medical benefit, patient groups suggested that there may be some instances where bypassing therapies were covered as a pharmacy benefit, and also stated that there may be general confusion about the different payment structures between pharmacy and medical benefits. Patients expressed concern about escalating patient out-of-pocket costs in the form of drug co-pays on top of co-insurance and deductibles even though patients with inhibitors already regularly reach their annual out-of-pocket maximums.

Prior Authorization Criteria

Prior authorization criteria varied among plans in their level of specific requirements for authorization. The most specific coverage policy we reviewed was from Harvard Pilgrim Health Care New England in their specialty guideline managed by CVS/Caremark. It requires laboratory documentation that the patient has high titer inhibitors.[62] Most other policies required self-attestation by a prescribing physician that the patient had inhibitors and required either prophylaxis or on-demand treatment with BPAs. Tufts Health Plan is an example of a more basic coverage policy.[63] Both policies are available in Appendix C.

2.2 Clinical Guidelines

National Hemophilia Foundation, Medical and Scientific Advisory Council Recommendations, 2013-2017[64-67]

https://www.hemophilia.org/Researchers-Healthcare-Providers/Medical-and-Scientific-Advisory-Council-MASAC/MASAC-Recommendations

The Medical and Scientific Advisory Board (MASAC) of the National Hemophilia Foundation (NHF) has issued several recommendations for the management of patients with severe hemophilia A. They recommend that such patients receive prophylactic treatment with clotting factor concentrates, and that prophylaxis be initiated before the onset of frequent bleeding. For patients with high titer inhibitors, prophylaxis with BPAs (either rFVIIa or aPCC) is considered to be optimal as it reduces the risk of joint-damaging bleeds, improves quality of life, and aids in the prevention of life-threatening bleeds. The MASAC notes that lifetime prophylactic therapy should be considered because it mitigates the risk of permanent joint damage, while noting that there are no definitive guidelines that address this question. In addition, the MASAC recommends that patients with inhibitors be prescribed and trained in the use of BPAs at home for both the prevention and treatment of bleeds. The availability of at-home treatment is considered to be of particular importance for patients undergoing ITI, as these patients may still experience bleeds.

The MASAC recommends the use of rFVIIa or aPCC for the treatment of bleeds in patients with inhibitors, and notes that the choice of agent should be guided by the type of inhibitor (i.e., low- or high-responding), inhibitor titer, bleed location, and prior response to treatment.

World Federation of Hemophilia, Guidelines for the Management of Hemophilia, July 2012[68]

https://www1.wfh.org/publication/files/pdf-1472.pdf

In their 2012 guideline, the World Federation of Hemophilia (WFH) recommends prophylaxis with factor products to prevent bleeding and joint destruction, particularly before participation in high-risk activities. However, the guidelines note that it is uncertain whether prophylaxis should continue in children as they mature into adults due to a paucity of studies addressing this issue. At-home therapy is recommended for appropriate patients to improve access to early treatment and decrease hospitalization due to delay in treatment.

The WFH recommends the use of either rFVIIa or aPCC to treat bleeds in patients with inhibitors who do not respond to factor treatment, as both treatments have demonstrated equal effectiveness at a population level, though the guidelines note that the choice of BPA should be individualized as a patient may respond better to one agent than the other. This decision should be guided by inhibitor titer, record of clinical response to the product, and the characteristics of the bleed.

British Committee for Standards in Haematology, January 2013[69]

http://onlinelibrary.wiley.com/doi/10.1111/bjh.12091/abstract

The British Committee for Standards in Haematology's 2013 guidelines recommend treatment of bleeding with aPCC or rFVIIa in patients with factor VIII inhibitors and laboratory evidence that they are unlikely to respond to factor VIII. Combination treatment with aPCC and rFVIIa should only be used to treat life- or limb-threatening bleeds that are unresponsive to monotherapy with either agent. All bleed management decisions should be guided by individual patient characteristics including bleed site/severity, previous response to BPA, and laboratory testing of inhibitor status.

The guidelines include a recommendation for BPAs for prophylaxis, especially in young children after their first hemarthrosis. For those expected to begin ITI, they recommend prophylaxis with rFVIIa and a trial reduction if there is measurable recovery in factor VIII. Prophylaxis may also be used for older patients who experience recurrent bleeds or progressive arthropathy. The choice of individual BPAs can be considered on a per-patient basis based on success of treatment, logistical requirements, and cost. The guidelines do not include any recommendation for testing to monitor and determine the BPA dose, as there are no validated lab tests used outside of a clinical trial setting.

3. Comparative Clinical Effectiveness

3.1 Overview

To inform our review of the comparative clinical effectiveness of prophylaxis with emicizumab in patients with hemophilia A and factor VIII inhibitors, we abstracted evidence from available clinical studies of this agent, whether in published or unpublished form (e.g. conference abstracts or presentations, FDA review documents). We focused on evidence of the efficacy, safety, and effectiveness of prophylaxis with emicizumab in comparison with no prophylaxis or prophylaxis with BPAs in our target population of hemophilia A patients with inhibitors to factor VIII who will not be treated with ITI or for whom ITI has been unsuccessful. Because we have more mature trial results for older patients than younger children, we evaluated the evidence for two main subgroups, defined by age:

1. Adolescents and adults (ages 12 and older)
2. Children (younger than 12 years)

Our review focused on assessing the intermediate and long-term outcomes assessed in trials, as well as reported harms. We sought evidence on the following outcomes:

Intermediate Outcomes

- Rates of bleeding events (including treated and untreated bleeds, joint bleeds, target joint bleeds)
- Burdens of therapy (e.g., frequency of administration, route of administration, pain, etc.)
- Joint damage
- Number of emergency department visits and number of inpatient days
- Hospitalization
- Opioid dependence
- Red cell transfusion requirement
- Adherence
- Additional patient reported outcomes (employment, disability status, social engagement, education attainment, missed days of work or school, anxiety, depression, overall well-being, as well as outcomes for family and caregivers, particularly for younger children with hemophilia A)

Key Measures of Clinical Benefit

- Patient-reported quality of life
- Functional outcomes (including mobility)
- Pain
- Mortality

Harms

- Thrombotic events
- Thrombotic microangiopathy
- Other

When reviewing clinical evidence in ultra-rare populations, ICER acknowledges the challenges of study design, recruitment, and availability of data on long-term outcomes. As such, when possible we aim to add to our findings specific context regarding areas of challenges in study design.

3.2 Methods

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on emicizumab for prophylaxis in patients with hemophilia A and factor VIII inhibitors followed established best research methods.[70,71] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[72] The PRISMA guidelines include a list of 27 checklist items, which are described further in Appendix Table A1.

We searched MEDLINE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials via the Ovid platform, and EMBASE directly via the EMBASE website. The most recent search was conducted on October 20, 2017. We limited each search 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 above.

To supplement the database searches, we performed a manual check of the reference lists of included trials and reviews and invited key stakeholders to share references germane to the scope of this project. Further details of the search algorithms, methods for study selection, quality assessment, and data extraction are available in Appendix Tables A2-3, Figure A1, and Table E1.

Study Selection

We included evidence on emicizumab from all relevant published clinical studies irrespective of whether they used a comparative study design. With respect to BPAs, studies were only included if they compared BPAs (e.g., rFVIIa vs. aPCC) for prophylaxis, or if they assessed BPAs (individually or in combination) for prophylaxis versus on-demand treatment. We excluded studies conducted in patients with acquired hemophilia or in patients taking short-term prophylaxis in preparation for surgery.

In recognition of the evolving evidence base for hemophilia A and factor VIII inhibitors, 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/icers-methods/icer-value-assessment-framework/grey-literature-policy/). We excluded abstracts which reported duplicative data available in published articles.

Data Synthesis and Statistical Analyses

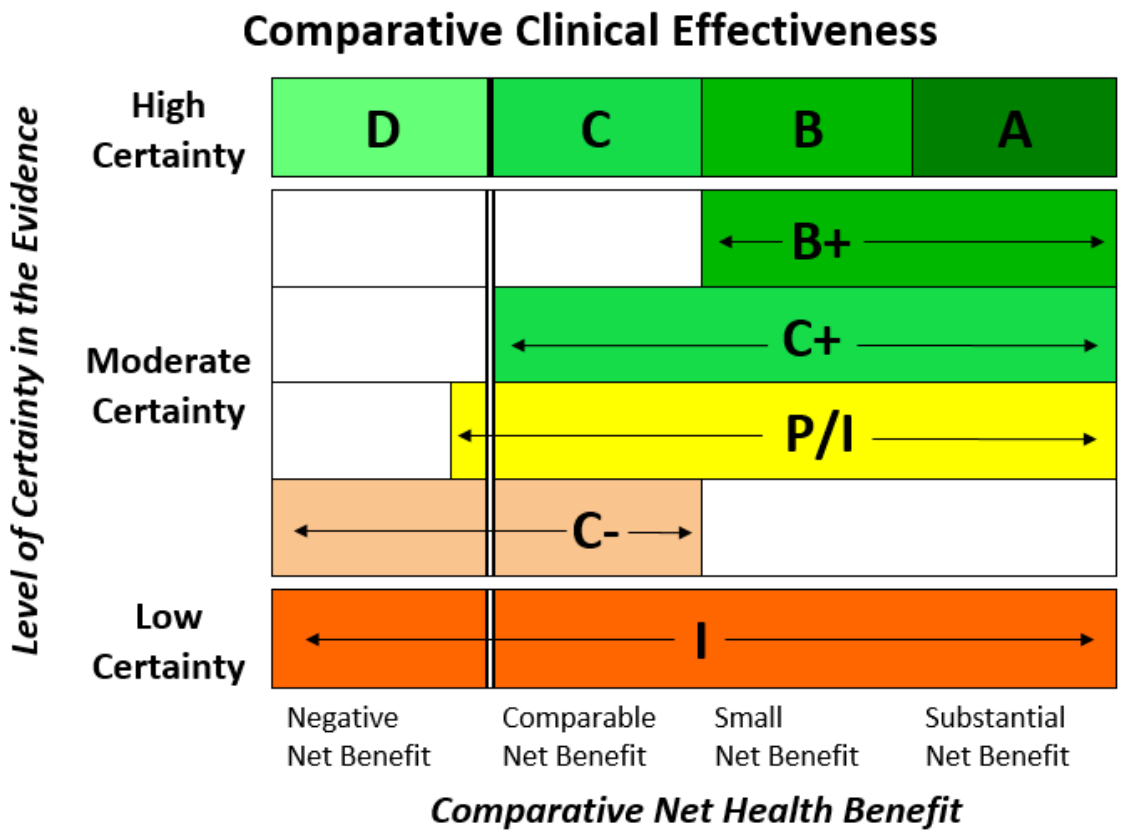
Data on relevant outcomes were summarized in evidence tables (see Appendix Table E1) and are synthesized in the text below. Due to major differences in study characteristics, study design, eligibility criteria, and outcomes assessed, we did not conduct a formal quantitative direct or indirect analysis of prophylaxis with emicizumab versus no prophylactic therapy or prophylaxis with BPAs.

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix (see Figure 3.1) to evaluate the evidence for a variety of outcomes. ICER does not change its approach to rating evidence for ultra-rare conditions. The evidence rating reflects a joint judgment of two critical components:

a) 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
b) The level of **certainty** in the best point estimate of net health benefit.[73]

Figure 3.1. 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 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 comparable, small, or substantial net health benefit, and a small (but nonzero) likelihood of a negative net health benefit
C- = "Comparable or Inferior" - Moderate certainty that the point estimate for comparative net health benefit is either comparable or inferior
I = "Insufficient" - Any situation in which the level of certainty in the evidence is low

Assessment of Publication Bias

As part of our quality assessment, we evaluated the evidence base 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 emicizumab using the clinicaltrials.gov database of trials. We scanned the site to identify studies completed more than two years ago that would have met our inclusion criteria and for which no findings have been published. Any such studies may have provided qualitative evidence for use in ascertaining whether there was a biased

representation of study results in the published literature. For this review, we did not find evidence of any study completed more than two years ago that that has not subsequently been published.

3.3 Results

Study Selection

Our literature search identified 3,318 potentially relevant references (see Appendix Figure A1), of which eleven references (seven publications and one abstract) relating to five trials met our inclusion criteria. Primary reasons for study exclusion included study populations outside of our scope (e.g., patients with hemophilia A without inhibitors, or patients with other types of hemophilia such as hemophilia B or acquired hemophilia), interventions not of interest, and indications not of interest (e.g., use in short-term prophylaxis before surgery). Two of the included trials assessed the efficacy of emicizumab, while the remaining trials were focused on the BPAs. Additional details of the included references are described in Appendix E, and the key studies are summarized in Table 3.1.

Quality of Individual Studies

Of the five identified trials, we did not assign a quality rating to one trial that has not yet been published (HAVEN 2). The remaining four trials were judged to be of good or fair quality using criteria from the US Preventive Services Task Force (USPSTF) (see Appendix E).[74] One of the trials (HAVEN 1) was given two quality ratings (the randomized comparison between emicizumab prophylaxis and no prophylaxis was judged to be of good quality, while the comparison between emicizumab prophylaxis and prior BPA use was judged to be of fair quality). See Appendix Table E1 for the other trial ratings. Trials of good quality had study arms that were comparable at baseline, authors employed valid instruments to evaluate outcomes, and differential attrition was not observed. Fair-quality studies reported slight imbalances in baseline characteristics, showed some differences in follow-up between trial arms, and used less reliable measurement instrument to assess outcomes. We did not assign a quality rating to references that were obtained from grey literature sources (e.g., conference proceedings).

Table 3.1. Key Trials

Key Trials	F/U Duration	Treatment Group	Patient Characteristics	Measures of Bleeding Outcome
Emicizumab Trials				
HAVEN 1*[13] Open-Label RCT Phase III	At least 24 weeks	No prior BPA prophylaxis 1.Emicizumab prophylaxis (A) 2. No prophylaxis (B) Prior BPA prophylaxis 3. Emicizumab prophylaxis (C)	N=109 Median age: 28 years Range age: 12-75 years Hemophilia A: 100% Severe hemophilia: 94% Presence of target joint: 70%	Model-based annualized bleeding rate (ABR)†
HAVEN 2‡[17] Open-Label Single-Arm Study Phase III	9 weeks (median)	1. Emicizumab prophylaxis	N=60 Median age: 7 years Range age: 1-15 years Hemophilia A: 100%	Model-based ABR‡
BPA Trials				
PROOF[18] Open-Label RCT Phase III	12 months	1. aPCC prophylaxis 2. No prophylaxis	N=36 Median age: 24 years Range age: 7-56 years Hemophilia A: 92% Severe hemophilia: 92% Presence of target joint: 75%	Median ABR
Pro-FEIBA[11] Randomized Crossover Trial	6 months	1. aPCC prophylaxis 2. No prophylaxis	N=26 Median age: 29 years Range age: 3-63 years Hemophilia A: 100% Severe hemophilia: 100% Presence of target joint: 75%	Mean number of bleeding events over 6 months
Konkle 2007[75] Double-Blind RCT	9 months	1. 90 mcg/kg rFVIIa prophylaxis 2. 270 mcg/kg rFVIIa prophylaxis Both groups compared to pre-prophylaxis period	N=22 Median age: 16 years Range age: 5-56 years Hemophilia A: 95% Severe hemophilia: 100% Presence of target joint: 95%	Monthly bleeding rate

ABR: annualized bleeding rate, BPA: bypassing agent, F/U: follow-up, RCT: randomized controlled trial

*Late enrollers received emicizumab prophylaxis in a fourth group not included in analysis

†Ongoing trial. Analysis as of May 8, 2017

‡ABR was calculated by using a negative binomial regression model to determine bleeding rate per day, which was then converted to an annual rate

Clinical Benefits

Rate of Bleeding Events with Emicizumab

Adolescents and Adults (Ages 12 and Older)

One randomized trial found that prophylaxis with emicizumab substantially reduced the bleeding events in adolescents and adults (ages 12 years and older) when compared to no prophylaxis. A substantial improvement with emicizumab prophylaxis was also observed in the trial period when compared to prior prophylaxis with BPAs.

We identified one phase III open-label RCT (HAVEN 1) that assessed the rate of bleeding events with emicizumab in 109 adults and adolescent males between the ages of 12 and 75 years with hemophilia A (any severity) and a history of a high titer factor VIII inhibitors (Table 3.1).[13] HAVEN 1 compared prophylaxis with emicizumab to no prophylaxis, and also used data from a previous prospective non-interventional study to compare emicizumab prophylaxis to BPA prophylaxis. Participants were included if they had six or more bleeds (if receiving on-demand treatment) or two or more bleeds (if on prophylactic BPA) in the previous 24 weeks before enrollment.[13] Those who had previously received on-demand treatment with a BPA but not prophylaxis were randomly assigned in a 2:1 ratio to receive emicizumab prophylaxis (group A; 3 mg/kg once weekly for four weeks, followed by 1.5 mg/kg once weekly thereafter) or no prophylaxis (group B), while those who had previously received prophylaxis with a BPA received emicizumab prophylaxis (group C) at the same dose as those in group A, and were included in the BPA prophylaxis comparison. [13]

Emicizumab Compared to No Prophylaxis

The primary outcome in the HAVEN 1 trial was the difference in the annualized bleeding rate (ABR) for "treated bleeds" between participants who received weekly emicizumab prophylaxis (group A; median follow up: 29 weeks) and those who received no prophylaxis (group B; median follow up: 24 weeks). The ABR for "treated bleeds" was significantly lower among patients randomized to emicizumab prophylaxis compared to the no-prophylaxis group (2.9 vs. 23.3; relative risk [RR]=0.13; $p<0.0001$), representing a relative risk reduction of 87% in bleeding events with emicizumab.[13] The ABR of "all bleeding events" (treated and untreated bleeds) was reported as a secondary outcome. Patients on emicizumab showed a statistically significantly lower rate for all bleeding events (treated and untreated bleeds) compared to those on no-prophylaxis (5.5 events vs. 23.3 events; RR=0.2, $p<0.0001$), representing a relative risk reduction of 80%.[13] Approximately 63% of all patients randomized to emicizumab had no bleeding during the follow up period, compared to 6% in the no prophylaxis group. Similarly, significant differences in favor of emicizumab compared to no prophylaxis were observed in the rates of other secondary bleeding related endpoints, including treated spontaneous bleeds, treated joint bleeds, and treated target joint bleeds (see Table 3.2).

These findings were consistent among the different age groups (< 18 years, > 18 years, < 65 years and > 65 years) and races (Asian, African-American, and white). Similarly, emicizumab prophylaxis resulted in less bleeding events irrespective of the presence of target joints or severity of symptoms prior to the start of the study.[13]

Emicizumab Compared to BPA Prophylaxis

HAVEN 1 investigators used bleeding events and safety data from a prior non-interventional study (NIS) to compare BPA prophylaxis to emicizumab prophylaxis. The NIS was a real-world prospective study, in which hemophilia A patients on episodic or prophylactic treatment with BPA were followed for six months.[13,76] As noted above, all patients who had previously received prophylactic treatment with a BPA were assigned to receive weekly emicizumab prophylaxis in a separate cohort (group C) of the HAVEN 1 trial. An intra-individual comparison was conducted among the patients in the cohort who had participated in the non-interventional study (n=24) by comparing each person's bleeding outcome during the prior non-interventional study while they were on BPA prophylaxis to their bleeding outcomes while on emicizumab. The analysis showed a significantly lower bleeding rate after 24 weeks on emicizumab prophylaxis when compared with previous BPA prophylaxis (ABR: 3.3 vs. 15.7, RR=0.21, p<0.0001), representing a relative risk reduction of 79%. After about one year, the ABR on emicizumab prophylaxis reduced to 2.1 representing a relative risk reduction of 87% (p<0.0001) when compared to prior prophylaxis with BPAs (see Table 3.3).[77]

Table 3.2. Bleeding Outcomes in the Randomized Arms of HAVEN 1

Bleeding Outcomes	Randomized Study Arms*		Emicizumab vs. No Prophylaxis	
	Emicizumab Prophylaxis (n=35)	No Prophylaxis (n=18)		
	ABR† (95% CI)		Risk Ratio	p Value
Treated Bleeds	2.9 (1.69, 5.02)	23.3 (12.33, 43.89)	0.13	<0.0001
All Bleeds (Treated + Untreated)	5.5 (3.58, 8.60)	28.3 (16.79, 47.76)	0.20	<0.0001
Treated Spontaneous Bleeds	1.3 (0.73, 2.19)	16.8 (9.94, 28.30)	0.08	<0.0001
Treated Joint Bleeds	0.8 (0.26, 2.20)	6.7 (1.99, 22.42)	0.11	0.0050
Treated Target Joint Bleeds	0.1 (0.03, 0.58)	3.0 (0.96, 9.13)	0.05	0.0002

ABR: annualized bleeding rate

*Other non-randomized study arms not presented

†ABR was calculated by using a negative binomial regression model to determine bleeding rate per day, which was then converted to an annual rate

Table 3.3. Emicizumab Prophylaxis Versus Prior BPA Prophylaxis in HAVEN 1 Trial

Median Efficacy Period for Emicizumab	N=24		Emicizumab vs. Prior BPA	
	Emicizumab Prophylaxis	Prior BPA Prophylaxis		
	ABR For Treated Bleeds* (95% CI)		Risk Ratio	p Value
24 Weeks	3.3 (1.3, 8.1)	15.7 (11.1, 22.3)	0.21	<0.001
55 Weeks	2.1 (0.9, 5.1)		0.13	<0.0001

ABR: annualized bleeding rate, BPA: bypassing agent

*ABR was calculated by using a negative binomial regression model to determine bleeding rate per day, which was then converted to an annual rate

Emicizumab in Children (<12 Years)

Interim results from one single-arm trial indicated that prophylaxis with emicizumab prevented bleeding events in most children. A substantial improvement with emicizumab prophylaxis was also observed in the trial period when compared to prophylaxis with BPAs during a prior observation period.

In children less than 12 years old, we identified one ongoing clinical trial (HAVEN 2) with an interim analysis available in a conference abstract that assessed the rate of bleeding events in children while on emicizumab (Table 3.1). HAVEN 2 is a phase III single-arm, open-label, multicenter trial enrolling pediatric male patients less than 12 years of age (or 12 to 17 years if < 40 kg) to receive emicizumab prophylaxis for at least 52 weeks.[17] Participants were enrolled if they had hemophilia A of any severity, a history of a high titer of factor VIII inhibitor and required treatments with BPAs. At the time of the interim analysis, 60 patients (median age: 7 years, range: 1-15 years) had been enrolled and followed for a median observation of nine weeks (range: 1.6 - 41.6).

The primary outcome in HAVEN 2 was the ABR of treated bleeding events. As secondary outcomes, HAVEN 2 also evaluated the ABR of other bleeding related outcomes including all bleeds (treated and untreated), treated spontaneous bleeds, treated joint bleeds, and treated target joint bleeds. The ABR analysis included only 23 patients that had been followed for up to 12 weeks. The ABR for "treated bleeds" and "all bleeds" (treated and untreated) was 0.2 (95% CI: 0.06-0.62) and 2.9 (95% CI: 1.75-4.94), respectively.[17] In addition, the majority of patients (65%) who are currently enrolled in HAVEN 2 have had zero treated bleeds. Other treated related secondary outcomes are presented in Table 3.4.[17]

Emicizumab Compared to BPA Prophylaxis

HAVEN 2 also compared the use of emicizumab prophylaxis to prophylaxis with BPA as a secondary outcome by using bleeding events and safety data from the same prior non-interventional study described in the section on HAVEN 1.[76] Thirteen of the 18 patients who had previously participated in the non-interventional study were included in an intra-individual comparison (prophylactic

treatment in 12 patients and on-demand treatment in one patient). The results showed a substantially lower bleeding rate after about 12 weeks on emicizumab prophylaxis when compared with previous BPA prophylaxis (ABR: 0.2 vs. 17.2, RR=0.01), representing a reduction of 99% (p-value not reported).[17]

Table 3.4. Bleeding Outcomes in HAVEN 2 Trial

	ABR (95% CI)	Number of Patients with Zero Bleeds (%)
Number of Patients Included in Analysis	23	57
Types of Bleed		
Treated Bleeds	0.2 (0.06, 0.62)	54 (94.7)
All Bleeds (Treated + Untreated)	2.9 (1.75, 4.94)	37 (64.9)
Treated Spontaneous Bleeds	0.1 (0.01, 0.47)	56 (98.2)
Treated Joint Bleeds	0.1 (0.01, 0.47)	56 (98.2)
Treated Target Joint Bleeds	--	57 (100)

ABR: annualized bleeding rate

Table 3.5. Emicizumab Prophylaxis Versus Prior BPA Prophylaxis in HAVEN 2 Trial

ABR on Emicizumab Prophylaxis (95% CI)	ABR on Prior BPA Prophylaxis (95% CI)	Risk Ratio	p Value
0.2 (0.1, 0.8)	17.2 (12.4, 23.8)	0.01	NR

ABR: annualized bleeding rate, BPA: bypassing agent

Bleeding Events in BPA Studies

We identified three clinical trials that assessed the rate of bleeding events on BPA prophylaxis (Table 3.1). However, we could not quantitatively compare BPAs to each other or to emicizumab due to the major differences in the patient populations and in the way the bleeding outcomes were presented in the studies (Table 3.6). Adults and pediatric population were included in two separate emicizumab trials, while the BPA trials included a mix of pediatric and adult patients. In addition, measures of bleeding outcomes also varied across studies. For example, bleeding events were presented as monthly bleeding rates in Konkle 2007, while they were presented as median ABRs in PROOF. Furthermore, none of the BPA studies clearly stated if the bleeding outcomes reported were "treated bleeds" or "all bleeds" (including untreated bleeds) as described in the emicizumab trials; however, we inferred from the description of the studies that the bleeding outcomes in the three BPA trials referred to treated bleeds. In addition, detection of events (such as bleeding events) was done with a mobile app in the HAVEN trials, while the method of detection was unclear in the earlier BPA trials.

Of the three BPA trials, two assessed the efficacy of aPCC (PROOF and Pro-FEIBA) and compared aPCC prophylaxis to no prophylaxis. The first aPCC trial (PROOF) presented the median ABR as a primary outcome. The median ABR was statistically significantly lower among patients who were

on aPCC prophylaxis compared to the no-prophylaxis group (7.9 vs. 28.7; RR=0.28; p=0.0003), representing a relative risk reduction of 72.5% in bleeding events.[18] In addition, two of the 17 patients on aPCC (12%) had zero bleeds over the study period (12 months), while none of the patients on no prophylaxis were free of bleeding episodes during the study. The median ABRs of other bleeding related endpoints were also significantly lower among patients on aPCC prophylaxis compared to no prophylaxis (Table 3.6). In the second aPCC trial (Pro-FEIBA), bleeding was assessed as the mean bleeding rate over six months, and was found to be statistically significantly lower during the prophylaxis period compared to the crossover no prophylaxis period (5 vs. 13.1; RR=0.38; p < 0.001), representing a 62% relative risk reduction (Table 3.6).[11]

In addition, we identified one clinical trial that assessed the efficacy of prophylaxis with rFVIIa (Konkle 2007). Konkle 2007 assessed the number of bleeds per month during a prophylaxis period with rFVIIa as compared to the pre-prophylaxis period. Compared to the pre-prophylaxis period, the use of 90 mcg/kg and 270 mcg/kg doses of rFVIIa during the prophylaxis period significantly reduced the monthly bleeding rate (90 mcg/kg rFVIIa: 5.6 vs. 3.0 [p<0.0001]; 270 mcg/kg rFVIIa: 5.3 vs. 2.2[p<0.0001]), resulting in relative risk reductions of 45% and 59%, respectively.[75] A similar trend was observed for joint bleeds (Table 3.6).

Table 3.6. Bleeding Outcomes in BPA Studies

Trial	BPA Type	Outcome		Risk Ratio*; p Value
PROOF	aPCC	***Median Annualized Bleeding Rate (ABR)*** *Prophylaxis vs. No Prophylaxis (IQR)*		
		Total bleeds†	7.9 (8.1) vs. 28.7 (32.3)	0.28; p=0.0003
		Spontaneous bleeds†	5.6 (5.1) vs. 18.9 (32.6)	0.30; p=0.0008
		Joint bleeds†	6.0 (7.1) vs. 22.9 (32.8)	0.26; p=0.0006
Pro-FEIBA	aPCC	***Mean Number of Bleeding Events Over Six Months*** *Prophylaxis vs. No Prophylaxis (SD)*		
		Total bleeds†	5.0 (5.0) vs. 13.1 (7.1)	0.38; p<0.001
		Joint bleeds	4.2 (4.3) vs. 10.8 (7.5)	0.38; p<0.001
		Target joint bleeds	NR	0.28; p<0.001
Konkle 2007	rFVIIa (90 mcg/kg, 270 mcg/kg)	***Monthly Bleeding Rate*** *Prophylaxis Period vs. Pre-Prophylaxis Period*		
		Total bleeds†		
		90 mcg/kg	3.0 vs. 5.6	0.55; p<0.0001
		270 mcg/kg	2.2 vs. 5.3	0.41; p<0.0001
		Target joint bleeds†		
		90 mcg/kg	NR	0.57; p<0.0001
		270 mcg/kg	NR	0.39; p<0.0001

ABR: annualized bleeding rate, BPA: bypassing agent

*Calculated from the reported percent reduction

†This is interpreted as treated bleeds based on the description in the study although not stated in the study

Health-Related Quality of Life and Other Outcomes

Emicizumab prophylaxis resulted in greater improvement in health-related quality of life as measured by Haem-A-QoL and EQ-5D-5L when compared to no prophylaxis; and improvement in caregiver burden as measured by inhib-QOL. Emicizumab also resulted in improvement in school and work attendance, and fewer hospitalized days when compared to no prophylaxis, although statistical significance for these outcomes were not reported. There were no data available for emicizumab regarding pain, joint outcome, or mortality. Prophylaxis with BPAs has not been shown to significantly improve health-related quality of life as measured by EQ-5D or Haem-A-QoL.

Haem-A-QoL

The Haem-A-QoL was measured as a secondary outcome in HAVEN 1. It assesses the health-related quality of life in adult patients with hemophilia, and is based on a scale of 0 to 100.[58] The difference between the Haem-A-QoL score in the emicizumab group and the no prophylaxis group in HAVEN 1 was statistically significant and larger than the minimum clinically-important difference (CID) of 10 points in the physical health subscale (21.6 [95% CI, 7.9 to 35.2], p=0.003) and seven points in the total score (14.0 [95% CI, 5.6 to 22.4], p=0.0020) at week 25.[13]

HAVEN 1 did not present any data on the Haem-A-QoL score for the comparison of emicizumab prophylaxis to prior BPA prophylaxis.

Patients in HAVEN 2 exhibited marked improvements from baseline to week 25 on the physical health subscale (Mean change: -19.6 [95%CI, -42.9 to 3.6]) and total score (Mean change: -9.8 [95%CI, -20.0 to 0.4]) on the modified Haem-A-QoL for children (Haem-A-QoL – short form). [78]

Only one of the BPA studies (PROOF) reported on Haem-A-QoL. At 12 months in the PROOF trial, although the change in Haem-A-QoL score from baseline favored the patients on aPCC prophylaxis compared to the no prophylaxis group, the observed difference between the two groups was not statistically significant and the absolute difference was smaller than the minimum CID.[18]

Inhib-QOL

Inhib-QOL is a 13-item questionnaire adapted to assess the health-related quality of life in hemophilia patients with inhibitors. This was used to assess the caregiver perception of child health and caregiver burden in HAVEN 2. Marked improvements from baseline to week 25 were observed in all the subdomains. The greatest improvement was observed on the physical health subscale (Mean change: -31.7 [95%CI, -43.4 to -20.0]), dealing with inhibitor (Mean change: -26.8 [95%CI, -34.9 to -18.8]), family life (Mean change: -25.8 [95%CI, -38.3 to -13.3]), and total score (Mean change: -21.8 [95%CI, -28.3 to -15.4]) as assessed by the caregivers.[78]

EQ-5D-5L

EQ-5D is a self-administered generic health-related quality of life instrument that can be used in a wide range of health conditions and treatments. The EQ-5D-5L expands the normal range of responses to each dimension from three to five levels. The instrument includes a visual analogue scale (VAS) that measures health-related quality of life on a scale of 0 to 100 and can also be converted to a utility score ranging from -0.4 to 1, with higher scores on both scales indicating a better health status. In HAVEN 1, EQ-5D-5L was measured as a secondary outcome. Compared to the no prophylaxis group, patients on emicizumab prophylaxis had statistically significantly higher VAS scores (observed difference: -9.7 [95% CI: -17.6 to -1.8], p=0.02) and index utility (observed difference: -0.16 [95% CI: 0.25 to -0.07] p=0.001) at week 25. The observed differences between the two groups were larger than the minimum CIDs (CID: VAS=7 points; Utility score=0.07 points).[13] HAVEN 1 did not present EQ-5D-5L results comparing emicizumab prophylaxis to BPA prophylaxis. There are currently no EQ-5D-5L results available from HAVEN 2.

All the BPA studies reported on EQ-5D and showed a trend towards improvement in favor of aPCC and rFVIIa prophylaxis. However, the improvements observed were not statistically significant and the absolute differences were smaller than the minimum CID when compared to the no prophylaxis group or the pre-prophylaxis period.[11,18,75]

Missed Work/School

In HAVEN 1, relative to the no prophylaxis group, patients on emicizumab prophylaxis had fewer missed days from school (33% vs. 4%) or from work (14% vs. 7%) over 25 weeks.[79] However, statistical significance was not reported. Similarly, patients in HAVEN 2 observed an improvement in school and daycare attendance at week 25 when compared to baseline attendance (Percentage of patients with no missed school/daycare days: 83.3% vs. 27.5% at baseline; p value was not reported).[78] In the PROOF and Pro-FEIBA trials, the mean number of days lost from school/work was lower among patients on prophylaxis with aPCC compared to those on no prophylaxis, (mean difference: PROOF, 8 days; Pro-FEIBA, 13 days).[18,80] Statistical significance was not reported. Similarly, the median number of absentee days from school or work was less during the prophylaxis period with rFVIIa compared with the pre-prophylaxis period (4.5 days vs. 18.5 days).[81] Statistical significance was also not reported.

Hospitalization

After 25 weeks of follow up in HAVEN 1, patients treated with emicizumab had fewer hospitalized days when compared to patients on no prophylaxis (mean hospitalized days: 1.9 vs. 4.2 days; p=NR)[79]PROOF found a similar number of hospitalized days between patients on aPCC prophylaxis and no prophylaxis.[18] There were no data on the impact of rFVIIa prophylaxis on overall rates of hospitalization; however Konkle 2007 reported a significant decrease in hospital days due to

bleeding with rFVIIa prophylaxis compared to the no prophylaxis period (1.5 vs. 9.5 days, p value was not reported).[75]

Pain

There have been no published data on the impact of emicizumab and rFVIIa prophylaxis on pain. Prophylaxis with aPCC was shown to result in a significant improvement from baseline on the 0 to 100 VAS pain scale at six months (Mean change [SD]: 20.3 [38.9], p=0.01) and 12 months (mean change [SD]: 23.2 [46.6], p=0.02). In contrast, there was no significant change in the mean VAS pain scale at six months and 12 months in the no prophylaxis group.[82] However, treatment groups were severely imbalanced with regard to mean baseline pain level (55.5 vs. 35.2 for aPCC and no prophylaxis, respectively).[82]

Joint Damage

HAVEN 1 and 2 did not report on the impact of emicizumab on joint damage. In PROOF, the range of motion in three key joints (ankles, knees, and elbows) was assessed at baseline and at six-month follow-up and was found to be improved and maintained in the two arms of the trial (aPCC prophylaxis and no prophylaxis). The difference between the two groups was not reported. Konkle 2007 also found the orthopedic joint score to be unchanged over the nine-month course of the trial. We did not identify any trial in patients with inhibitors to factor VIII that assessed the long-term effects of prophylaxis on joint damage.

Mortality

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

Other Outcomes

We did not identify any studies that assessed the impact of prophylaxis with emicizumab or BPAs on the other outcomes of interest, including emergency department visits and inpatient days, opioid dependence, red cell transfusion requirements, adherence, and other patient-related outcomes (such as employment, disability status, social engagement, education attainment, anxiety, depression, overall well-being, as well as outcomes for family and caregivers, particularly of younger children with hemophilia A).

Harms

Emicizumab

The most common observed side effect of emicizumab was injection site reaction. An increased risk of thrombotic microangiopathy and thrombotic events were observed in patients on emicizumab who received large and multiple doses of aPCC for treatment of bleeding events.

About 70% of patients on emicizumab prophylaxis experienced one or more adverse events. The most common treatment-related adverse event (AE) in both HAVEN 1 and 2 was injection site reaction, occurring in 15% to 17% of patients on emicizumab prophylaxis.[13,17] Most of these were reported to be mild in intensity, except for one case that lasted for 26 days. Other common AEs occurring in ≥ 5% of patients in HAVEN 1 and HAVEN 2 were upper respiratory tract infection, headache, fatigue, and arthralgia. Serious AEs occurred in 9-11% of patients on emicizumab prophylaxis and included thrombotic microangiopathy in three patients (two cases resolved following discontinuation of aPCC; one patient died (from recurrent rectal hemorrhage which was considered not to be related to the use of Emicizumab)). In addition, cavernous sinus thrombosis occurred in one patient, and skin necrosis (and superficial thrombophlebitis) in one patient; both cases did not require anticoagulation. All thrombotic microangiopathy and thrombotic events occurred in HAVEN 1 in patients who had received multiple doses of aPCC for bleeding (averaged more than 100 U/kg) while on emicizumab prophylaxis.[13] There was no thrombotic microangiopathy or thromboembolic events or any serious adverse events (SAEs) deemed to be treatment related in preliminary reports from HAVEN 2.[17]

Given the thrombotic microangiopathy and thrombotic events in HAVEN 1, the FDA placed a boxed warning for thrombotic microangiopathy and thromboembolism in the label for emicizumab, noting that benefits and risks must be considered before using aPCC in patients receiving emicizumab, and to discontinue aPCC and suspend dosing of emicizumab if such events occur.[21]

BPAs

Table 3.7 provides a summary of the AEs reported in the BPA prophylaxis studies. Between 55% and 70% of patients on aPCC prophylaxis experienced one or more AEs in the trials identified,[11,18] while 73-82% of patients on rFVIIa prophylaxis experienced an AE.[75]

In the aPCC trials, poor venous access (3%), catheter-site hemorrhage (6%), and catheter-site infection (9%) were the most common treatment-related AEs.[11] There was also one case each of allergic reaction to the study drug in the two aPCC trials.[11,18] Other common AEs included anemia, pain, fever, cough, diarrhea, nausea, vomiting, and ecchymosis.[11,18,83] None of the AEs noted in the rFVIIa study were deemed to be treatment related.[75]

There were no reports of thrombotic microangiopathy or thromboembolism in any of the BPA prophylaxis trials included in this review. However, thromboembolic events have been observed in other trials and safety surveillance studies. We identified one study that conducted a four-decade cumulative review of the safety databases of an aPCC manufacturer for all spontaneous and literature cases of thromboembolic events.[19] The study reported 85 cases of thromboembolic events in patients with hemophilia. Of the 85 events, 13 were reported as deep vein thrombosis and/or pulmonary embolism, 32 as myocardial infarction, 18 as disseminated intravascular coagulation, and 22 as other events.[19] In 31 of the events, rFVIIa was being used as a concomitant medication. In another study that reviewed the safety of rFVIIa in patients with congenital hemophilia using data from clinical trials and registries, a total of three thromboembolic events (cerebral infarction, central venous occlusion, and arteriovenous fistula occlusion) were identified in 8,758 episodes of use of rFVIIa (0.034%).[20]

Based on data from post-marketing surveillance, a boxed warning for thromboembolism was included in the aPCC FDA label, noting that cases of thromboembolism have been observed in patients receiving high doses of aPCC, individuals with thrombotic risk factors, or both.[83] Similarly, the rFVIIa prescribing label includes a boxed warning for thrombosis (serious arterial and venous thrombotic events) based on data from post-marketing surveillance and other clinical trials.[84]

Table 3.7. Adverse Events of Emicizumab, aPCC, and rFVIIa

	Emicizumab[13,17]	aPCC[11,18]	rFVIIa[75]
Number of Trials	2	2	1 (2 doses)
Patients with Any AE	70%	55-70%	73-82%
Patients with Any SAE	9 - 10%	13-29%	0-36%
Grade ≥ 3 AEs	8%	NR	NR
Treatment Related AE	22%	NR	0-18%
Thrombotic/Thromboembolic	0 -2.7%	0*	0*
Thrombotic Microangiopathy	0 – 2.7%	0	0
Drug Hypersensitivity	0	3-6%	0*
Catheter Site Infection	0	9%	0
Catheter Site Hemorrhage	0	6%	0
Injection Site Reaction	15 – 17%	0	0

AE: adverse event, SAE: serious adverse event

*Events have been reported in other trials and post-marketing surveillance (see preceding text for details)

Controversies and Uncertainties

Emicizumab is a new therapy with a novel mechanism of action. We lack long-term safety data, and it is possible that so-far undetected toxicities and adverse events will be encountered over time,[22] or that the rates of thrombotic microangiopathy and thrombotic events will be higher than seen in the clinical trials. As a novel therapy for an ultra-rare disorder, it is not surprising that we lack such evidence for emicizumab.

There were three cases of thrombotic microangiopathy and two thrombotic events that occurred in patients who received greater than 100 U/kg daily of aPCC for 24 hours or more for breakthrough bleeding in HAVEN 1. Whether it is safe to use aPCC in lower doses or for less time is uncertain given the small numbers of bleeds studied. While such events were not seen in HAVEN 1 with rFVIIa, this does not prove that such events cannot occur.

We assumed that prophylaxis with aPCC and rFVIIa are equally effective. There are no head-to-head randomized trials examining this issue. A randomized trial comparing aPCC and rFVIIa for treatment of bleeding found them to have similar efficacy.[85]

We have only observational data comparing emicizumab prophylaxis with BPA prophylaxis; the intra-study data compare emicizumab when it was administered as part of a clinical trial to BPA prophylaxis measured before the intervention period began.[13,17] As such, patients may have been more adherent to therapy during the interventional time period, which would tend to make emicizumab appear more effective than BPAs.

The open-label design of HAVEN 1 raises particular concerns for subjective outcome measures such as quality of life. Additionally, even for a seemingly "hard" outcome like treated bleeds, the decision to treat bleeding may have been influenced by patient and clinician knowledge of whether a patient was receiving emicizumab.

Results from HAVEN 2 are preliminary. It appears that pediatric patients receive at least as great a benefit from emicizumab as adolescents and adults. Point estimates from HAVEN 1 and 2 suggest that the benefits in pediatric patients may be greater than those in older patients, however further results are needed from HAVEN 2 to confirm or refute this. Even when these results become available, however, we will not be able to fully understand the incremental benefits of emicizumab given the single-arm nature of this study.

We found limited evidence on patient-reported outcomes, and no evidence on long-term clinical benefits such as potentially decreased joint damage and lowered mortality with prophylaxis in patients with inhibitors to factor VIII. While we modeled a decrease in joint damage with reduced bleeding, we assumed no reduction in mortality given the lack of data. If reductions in bleeding with prophylaxis correlate with reduction in mortality, the relative benefit with emicizumab will be larger than estimated in our modeling.

How emicizumab fits in with prophylaxis strategies that could include ITI has not been adequately assessed and is not addressed in this report. As experience is gained with emicizumab it might be used to defer or replace ITI, but the efficacy and safety of such an approach is uncertain.

Bleeding events were not consistently defined and recorded across trials, making inter-trial comparisons difficult. We heard a concern that there had been secular trends since the BPA trials where clinicians and patients were told in the past to treat all bleeds and more recently to only

treat bleeds if this were clearly necessary. This could lead to fewer treated bleeds in more recent trials. However, recording of bleeds appeared to be more comprehensive in HAVEN 1 than in earlier trials, so this could have led to more untreated bleeds being detected. To address this concern, we included a scenario analysis with multiple assumptions favoring BPAs in our economic model ("BPA-favoring scenario"), where we assumed that the reduction in treated bleeds with emicizumab was only as great as the reduction seen in HAVEN 1 for all bleeds. The BPA-favoring scenario (Appendix Tables F8-F9) was also designed to deal with the following concerns:

- Clinicians may decide it is necessary to only treat bleeds on emicizumab prophylaxis with rFVIIa, which is more expensive than aPCC. In the BPA-favoring scenario, we assume all bleeds on emicizumab are treated with rFVIIa and all bleeds on aPCC prophylaxis are treated with aPCC.
- We do not have adherence data on emicizumab, while adherence to aPCC in Antunes 2014 was 88%. For the BPA-favoring scenario (and the base case), we assume emicizumab adherence to be 100% and aPCC adherence to be 88%.
- Despite treating bleeding events on emicizumab only with rFVIIa, we continue to assume the rate of thrombotic microangiopathy and thrombotic events that were seen in HAVEN 1.

The safety of emicizumab has not been evaluated in many clinical settings that could affect coagulation or the need for coagulation. These include sepsis, head trauma, major trauma, and the presence of central lines.

3.4 Summary and Comment

Methodologic limitations in trials of emicizumab include relatively short follow-up and the lack of head-to-head randomized comparisons with BPAs. Given that this patient population is small enough to qualify as ultra-rare, a head-to-head study versus a BPA would not be expected for regulatory approval. Despite these limitations, we find that:

- In adults, prophylaxis with emicizumab is efficacious in reducing bleeding events compared with no prophylaxis and improves quality of life. Observational data collected in the HAVEN 1 trial suggest that emicizumab is more effective in reducing bleeding events than prophylaxis with BPAs (aPCC and rFVIIa).
- In children, observational data collected in the HAVEN 2 trial suggest that emicizumab is more effective in reducing bleeding events than prophylaxis with BPAs. BPA prophylaxis reduces bleeding events compared with no prophylaxis, so we conclude that emicizumab also reduced bleeding events compared with no prophylaxis.
- Long-term outcomes were not measured in the trials of emicizumab. It is possible that reducing bleeding events will also reduce joint damage and lower mortality.

- The safety of any new therapy is an important consideration, and a small number of patients experienced thrombotic microangiopathy and thrombotic events with emicizumab. While there is a suggestion that these may only occur when patients are also treated with high doses of aPCC, there is still relatively little experience with emicizumab prophylaxis. The safety of emicizumab in patients experiencing events that can alter coagulation or the need for coagulation, such as sepsis or major trauma, has not been assessed. We also have more limited evidence on safety in patients younger than age 12 than in older patients.
- Although not directly reported in trials, emicizumab is substantially less burdensome for patients and families than BPAs. Emicizumab is administered by subcutaneous injection once per week, while BPAs are administered by intravenous infusion multiple times per week.

In summary, for people ages 12 and older with hemophilia A with inhibitors who will not be treated with ITI or for whom ITI has been unsuccessful, we have high certainty that emicizumab provides a substantial net health benefit ("A") compared with no prophylaxis. This reflects our belief that the large reductions in bleeding events exceed possible harms from thrombotic microangiopathy and thrombotic events. Given limitations in evidence on the safety of emicizumab, as well as only observational data comparing emicizumab with BPAs in all patients, and comparing emicizumab with no prophylaxis in children, our certainty of the net health benefit for these comparisons is somewhat smaller. Despite this, given the results of the trials and the reduced burden with emicizumab, for children younger than 12 we have high certainty that emicizumab provides at least a small net health benefit ("B+") compared with no prophylaxis, and in adults and children we have high certainty that emicizumab provides at least a small health benefit ("B+") compared with prophylaxis with BPAs.

4. Long-Term Cost Effectiveness

4.1 Overview

The primary aim of the long-term cost effectiveness analysis was to estimate the cost-effectiveness of emicizumab as prophylactic therapy for patients with hemophilia A and inhibitors to factor VIII, using a *de novo* health economic model. This model compared emicizumab to two alternative strategies: 1) prophylaxis with BPAs and 2) no prophylaxis. For all three strategies, patients were treated with BPAs during a bleeding episode. The model outcomes were expressed in terms of life years, quality-adjusted life years (QALYs), number of bleed events, and total costs over a lifetime horizon. Future costs and outcomes were discounted at 3% per year. Under the conditions of ICER's ultra-rare disease framework, we considered "dual base cases," which reflect the health system and societal perspectives, respectively. The societal perspective included the impact of the treatment on patient and caregiver productivity and other indirect costs, such as travel and accommodations for clinic and hemophilia treatment center (HTC) visits.

4.2 Methods

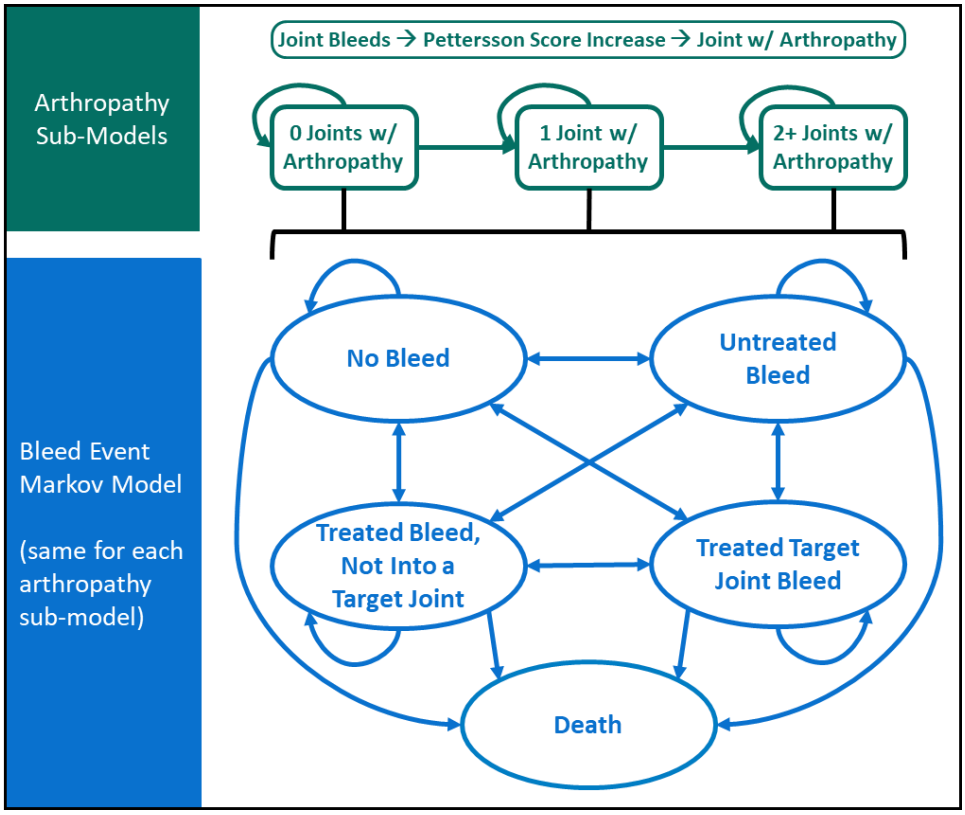
Model Structure

The decision-analytic model was structured to track various bleed events, the development of target joints and arthropathy, and survival over time for a cohort of hemophilia A patients with inhibitors (Figure 4.1). We chose a Markov model structure given the recurrent nature of bleeds. Because target joint-related arthropathy has a pronounced, long-lasting impact on quality of life, resource utilization, and costs, including but not limited to the impact of joint replacement surgery, we separated patients into three Markov sub-models based on the number of arthropathic joints within the overall model; the sub-models are "0 Joints with Arthropathy," "1 Joint with Arthropathy," and "2+ Joints with Arthropathy." This allowed assigning different sets of costs and utilities in each sub-model, specific to the level of arthropathy, while circumventing the "memory-less" characteristic of Markov models that considers patients homogeneous once in the current health state, irrespective of transitions from preceding states. Each sub-model included the same health states and bleed state transitions were equivalent.

For each treatment regimen, a hypothetical patient population entered the overall model distributed among the three "Joint with Arthropathy" sub-models based on the reported number of target joints from HAVEN-1. In each model cycle, a proportion of patients irreversibly transitioned from left to right as depicted in the "Joint with Arthropathy" sub-models section of Figure 4.1. Patients in each sub-model began in the "No Bleed" health state, where they remained until death or experiencing a bleed event that transitioned them to one of three Markov bleed states: "Untreated Bleed", "Treated Bleed Not Into a Target Joint", or "Treated Target Joint Bleed" (with

target joint defined as a single joint with three or more spontaneous bleeds into it within a consecutive six-month period)[37] (Figure 4.1). The transition between "Joint with Arthropathy" sub-models was linked to the frequency of joint bleeds and subsequent increase in Pettersson score.[23] All patients were modeled until they died due to disease- or non-disease-related causes. The model was developed in Microsoft Excel.

Figure 4.1. Model Framework



Target Population

Consistent with the population of focus in the clinical trials of emicizumab,[13,17] the population of interest in the model was male hemophilia A patients with inhibitors to factor VIII who will not be treated with ITI or for whom ITI was unsuccessful. We evaluated adolescents and adults aged 12 years and older (median age of 37 years, weighted by the sample size of arms A and B in the HAVEN trial) separately from children under 12 years of age (median age of 8.5 years).

Treatment Strategies

The intervention assessed in this model was emicizumab for prophylaxis. Patients were treated with BPAs (rFVIIa or aPCC) during a bleed episode (both into and not into a target joint) while on prophylaxis with emicizumab. We compared prophylaxis with emicizumab to two alternatives: 1)

prophylaxis with a BPA, and 2) no prophylactic therapy. As in the case of the intervention, for each comparator, bleeds are also treated with BPAs.

Key Model Characteristics and Assumptions

- The model utilized data from the HAVEN 1[13] (age 12 years and older) and HAVEN 2[17] (under 12 years old) trials to derive effectiveness estimates for bleed event prevention for emicizumab prophylaxis and no prophylaxis.
- The model assumed that aPCC and rFVIIa are equally effective and utilized effectiveness estimates for bleed event prevention with BPA prophylaxis (aPCC and rFVIIa combined) from the PROOF trial.[18]
- Survival was weighted by health state utilities derived from the published literature.[24-27,86] The model included separate utilities for different types of bleed events, and decreasing baseline utility tied to increasing arthropathy as defined by Pettersson score.
- The model included all direct treatment costs associated with each individual regimen, including drug acquisition costs and non-pharmacy costs (including all medical expenses except for drugs/clotting factor).[17,31,33]
- Under the conditions of ICER's ultra-rare disease framework, we considered dual base cases to reflect both the health system and societal perspectives. The societal perspective included the impact of the treatment on patient and caregiver productivity, as well as and other indirect costs such as travel and accommodations.
- Costs and outcomes were estimated over a lifetime time horizon using weekly cycles to capture the potential lifetime impacts of short-term and ongoing morbidity and mortality.
- All costs that were reported prior to 2017 were adjusted for inflation[87] and the equivalent estimate for the year 2017 is used in the model. Costs and outcomes were discounted at 3% per annum.[88]

Table 4.1. Key Model Assumptions and Rationales

Assumption	Rationale
A patient could transition to any bleed health state or to death from any of the other health states during each model cycle.	Reported trial data do not include transitions from one type of bleed to another. Any type of bleed could feasibly follow another type from week to week.
A patient could transition from the "0 Joints with Arthropathy" sub-model to the "1 Joint with Arthropathy" sub-model, and from there to the "2+ Joints with Arthropathy" sub-model, but not in the opposite direction.	Intra-articular bleeding (hemarthrosis) leads to synovial hypertrophy and cartilage damage (arthropathy), which manifests as gradual and irreversible joint destruction.
Bleed event rates are equivalent in all three "Joint with Arthropathy" joint sub-models.	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.
Joint replacement surgery could only occur in the patients with at least one joint with arthropathy.	The development of joint arthropathy is a precondition for joint replacement surgery.
Treatment adherence was assumed to be 100% for emicizumab prophylaxis and 88% for BPA prophylaxis.[18]	There are limited data on long-term adherence to emicizumab, so we conservatively assumed 100% adherence was required to achieve the results seen in HAVEN 1 and 2. For BPA, we applied the adherence rates as reported in Antunes. Adherence was varied in scenario analyses.
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 and are unlikely to develop inhibitors.
When pediatric patients (modeled efficacy estimates from HAVEN 2) reached the age of 12 years, their reduction in bleeding rate with emicizumab became that of patients aged 12 years and over (modeled efficacy estimates from HAVEN 1).	Data on the persistence of emicizumab's treatment effect in a patient cohort < 12 years old aging into ≥ 12 years old are not available. A scenario analysis explores the impact of assuming bleeding reduction persists at the childhood reduction level (0.01).
We based the starting distribution of prevalent arthropathy joints on HAVEN 1 and HAVEN 2 demographic data for all model comparators.	70% of patients aged 12 years or older had at least one arthropathy joint, and 70% of those patients had more than one arthropathy joint.[13] Among children under 12, 25% had at least one arthropathy joint, and 60% had more than one.[17]
The starting Pettersson score for all patients who began in the "0 Joints with Arthropathy" sub-model was assumed to be zero. Patients who began in the other two arthropathy joint sub-models were assigned a starting Pettersson score according to age at model entry.[23]	The incidence of arthropathy increases with age, and patients with arthropathic joints have a higher Pettersson score. The existing population of hemophilia A patients with inhibitors is wide-ranging in age and thus has varying levels of lifetime exposure to arthropathy-causing bleed events.
Pettersson score and joint arthropathy development increase as a function of joint bleeds (treated and/or untreated) over time. Joint bleeds are modeled separately to drive sub-model transitions and were assumed to be 60% of all bleeds (for each comparator) in base case analyses.	Pettersson score has been shown to increase by one point for every 12.6 joint bleeds (treated and/or untreated).[23] The proportion of all bleeds that are joint bleeds is explored in a scenario analysis.
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 the week to reflect that the impact of the bleed on utility lingers after the bleeding stops. The number of days/week for bleed utilities is varied in a scenario analysis.	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.
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 prophylaxis versus those not.

Model Inputs

Clinical Inputs

Bleed Events

A Markov model structure requires that health states be mutually exclusive, but the HAVEN 1 and 2 ABR outcomes were not mutually exclusive.[13,17] Thus, we used the all bleeds, BPA-treated bleeds, and target joint bleeds data to derive the mutually-exclusive bleed event probabilities used in the Markov model. Modeled bleed events (see Figure 4.1) were derived from trial-reported annualized bleed rates as follows:

- Untreated bleeds = all bleeds minus BPA-treated bleeds
- Treated bleeds not into a target joint = treated bleeds minus treated target joint bleeds
- Target joint bleed rates as reported by the trial publications

We modeled the no prophylaxis comparator's ABRs as observed in the no prophylaxis arm of the HAVEN 1 trial, assuming no prophylaxis patients age < 12 had the same rates as patients ≥ 12 years due to HAVEN 2's single-arm status and a lack of findings from other clinical studies for the younger age group. To model analogous bleed events for emicizumab prophylaxis patients, we applied rate ratios to the no prophylaxis comparator's ABRs; the rate ratios for patients ≥ 12 years old were reported in HAVEN 1, whereas rate ratios for patients < 12 were derived from the rate differences between HAVEN 1 and HAVEN 2. For BPA prophylaxis, we modeled a 72.5% reduction (rate ratio = 0.275) versus the no prophylaxis comparator for all bleed types based on the Antunes et al. trial.[18]

After deriving the mutually-exclusive ABRs needed for the model, we then converted them to weekly transition probabilities for each bleed event health state.

Table 4.2. Clinical Inputs

Trial Outcomes: Age 12+ years	Reported Trial Result	Trial-Derived Outcomes for Model	Derived ABR	Conversion to Weekly Probability	One-Year Cumulative Bleeds
All Bleeds		**Untreated Bleeds**			
ABR: No Prophylaxis[13]	28.3	No Prophylaxis	5.0	0.091	4.8
RR: Emicizumab Prophylaxis[13]	0.20	Emicizumab Prophylaxis	2.6	0.049	2.6
RR: BPA Prophylaxis[18]	0.275	BPA Prophylaxis	1.4	0.026	1.4
BPA-Treated Bleeds		**Treated Bleeds, Not into a Target Joint**			
ABR: No Prophylaxis[13]	23.3	No Prophylaxis	20.3	0.322	16.8
RR: Emicizumab Prophylaxis[13]	0.13	Emicizumab Prophylaxis	2.9	0.054	2.8
RR: BPA Prophylaxis[18]	0.275	BPA Prophylaxis	5.6	0.101	5.3
Treated Target Joint Bleeds		**Treated Target Joint Bleeds**			
ABR: No Prophylaxis[13]	3.0	No Prophylaxis	As reported	0.056	2.9
RR: Emicizumab Prophylaxis[13]	0.05	Emicizumab Prophylaxis	0.15	0.003	0.1
RR: BPA Prophylaxis[18]	0.275	BPA Prophylaxis	0.825	0.016	0.8
Trial Outcomes: Age <12 years	**Reported Trial Result**	**Trial-Derived Outcomes for Model**	**Derived ABR**	**Conversion to Weekly Probability**	**One-Year Cumulative Bleeds**
RR All Bleeds[13,17]	0.13	Untreated Bleeds	3.2	0.060	3.1
RR BPA-Treated Bleeds[13,17]	0.02	Treated Bleeds, Not into a Target Joint	0.5	0.009	0.5
RR Target Joint Bleeds[13,17]	0.00	Treated Target Joint Bleeds	0.0	0.000	0.0

ABR: annualized bleed rate, BPA: bypassing agent, RR: rate ratio

Arthropathy

We based the starting distribution of prevalent arthropathy joints on HAVEN 1 and HAVEN 2 demographic data for all model comparators. The starting distribution for 0, 1, and 2+ "Joint with Arthropathy" sub-models for each comparator was 30%/21%/49% for adults, and 75%/10%/15% for children, respectively. New arthropathy development and joint replacement surgery are driven by increases in the Pettersson Score to reflect the degree of arthropathy over time (minimum score 0 for joints without signs of arthropathy, to a maximum score of 78 points). The Pettersson score is a

validated radiological scoring system assessing the sum per patient of the total osteochondral changes in knees, elbows and ankles.[89] The reported relationship between Pettersson score is a one point increase in the Pettersson score per 12.6 joint bleeds, on average (95% CI: 11.1 – 14.7).[23] As such, the percentage of patients who received joint replacement surgery was based on the number of joint bleeds experienced by a patient. In line with the approach utilized by Fischer et al. and Earnshaw et al., we assumed that patients who reach a threshold for clinically-relevant damage (a Pettersson score of 28) require orthopedic surgery.[32,90] As in Earnshaw et al., we assumed that no patients over the age of 80 would undergo joint replacement surgery. Based on stakeholder input, we assumed that joints receiving orthopedic surgery required follow-up/maintenance surgical procedures every 20 years;[44] this assumption included additional cost and disutility for each repeat procedure.

Mortality

Mortality was based on the age-adjusted male US population; the annual probability of dying reported in US life tables[91] was converted to weekly probabilities of dying for each age. We then modeled the increased rate of death for hemophilia A patients with inhibitors, which was derived from a retrospective study of 7,386 males with severe hemophilia A over a 13-year period that reported a 70% increased odds of death for inhibitor patients.[7] We converted the reported odds ratio to a relative risk in the model, and then applied it to the background weekly probability of death for each model cycle. A detailed table of weekly mortality probabilities by age is available in Appendix Table F10.

Utilities

Health state utilities were derived from published literature sources and applied to the relevant health states. All utilities used in the model were measured in patients with hemophilia A using generic instruments, including EQ-5D,[24,25,27] SF-6D,[26] and standard gamble.[86] We used consistent health state utility values across treatments evaluated in the model. As stated above, bleed-associated utilities were applied in full for two days, followed by an average of "No Bleed" and "Bleed" utilities for five days. 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. The baseline utility was 0.82 for patients in the "No Bleed" health state in the "0 Joints with Arthropathy" sub-model; a treated bleed event received a utility of 0.66.[24] A treated bleed into a target joint received an additional disutility of -0.12.[25] The "No Bleed" utilities used in the "1 Joint with Arthropathy" and "2+ Joints with Arthropathy" sub-models were based on a study of the association of Pettersson score with quality of life (short form six dimension [SF-6D] utility scores);[26] we modeled the "No Bleed" utility in these two sub-models to reflect the increasing Pettersson score over time. Concurrently in these two sub-models, we proportionally adjusted downward the utility for treated bleeds as the "No Bleed" utility declined. Lastly, we included a disutility for orthopedic surgery, lasting for one month at the time of the procedure.[27]

Table 4.3. Utility Values for Health States

Parameter	Value
Utility: Hemophilia A With Inhibitors, No Bleed[24]	0.82
Utility: Hemophilia A With Inhibitors, Treated Bleed Not Into A Target Joint[24]	0.66
Utility: Hemophilia A With Inhibitors, Target Joint Bleed*[25]	0.54
Utility: No Bleed With Arthropathy, By Pettersson Score (PS)[26]	
• **PS 0-4**	0.82
• **PS 4-12**	0.82
• **PS 13-21**	0.79
• **PS 22-39**	0.73
• **PS 40-78**	0.72
Disutility: Orthopedic Surgery[27]	-0.39

*Calculated as utility of "hemophilia A patients with inhibitors, treated bleed not into a target joint" (0.66) minus disutility "hemophilia A with inhibitors, target joint bleed" (-0.12)

Economic Inputs

All costs were reported in 2017 dollars and adjusted for inflation when necessary.[87]

Drug Utilization

Patient weight, a key component of drug utilization, was varied according to age based on data from the Centers for Disease Control.[28] A detailed table of weight by age is available in the Appendix (Table F10).

The schedule of doses for each drug in each prophylaxis regimen, as well as protocol dosage for the indication, was used to model drug utilization and associated costs (Table 4.4).

Table 4.4. Treatment Regimen Recommended Dosage

Intervention	Dosage Forms and Strength	Prophylaxis Dosing	Bleed Event, On Demand Dosing
Emicizumab[13,17,21]	Single-dose vials of 30 mg/ml, 60 mg/0.4ml, 105 mg/0.7 ml and 150 mg/ml	3.0 mg/kg weekly for the first four weeks, followed by 1.5 mg/kg weekly	N/A
rFVIIa[75,81,92]	Single-use vials of 1, 2, 5, or 8 mg	90 mcg/kg daily	90 mcg/kg every 2 hours, adjustable based on severity of bleeding until hemostasis is achieved 90 mcg/kg every 3-6 hours after
aPCC[18,83]	500, 1000, or 2500 units per vial	85 units/kg every other day	50-100 units/kg every 6-12 hours until pain/disabilities and/or bleeding is resolved.*

*Not to exceed 20,000 units in any 24-hour period because of thrombosis risk (unrelated to emicizumab).

The cost of on-demand treatment with BPAs for bleed events was equivalent for all three modeled comparators. This estimate was based on the observed average units/kg (both rFVIIa and aPCC) from the HAVEN 1 trial.[13] We used a weighted average approach to combine arms A and B from HAVEN 1 to derive the overall estimate (Table 4.5). A detailed table of weekly prophylaxis and on-demand BPA treatment per bleed cost by age and weight is available in the Appendix (Table F10).

Table 4.5. Derivation of BPA On-Demand Treatment Costs per Bleed Event

	Number of Patients	Proportion	Units/kg	Total Units per Bleed*#	Cost/Bleed*	Combined*	Weighted Avg. Cost*
aPCC	89	33%	131.15	9,837	$19,122		$50,589
rFVIIa	141	52%	294.79	22,109	$44,413		
Both, aPCC	40	15%	297.30	22,297	$43,346	$142,370	
Both, rFVIIa			657.27	49,295	$99,024		

*Estimates shown are for a 75-kg patient. In the model, these estimates are based on patient age-based weight during each model cycle, thus the weighted average cost changes over time.

#The total dose of aPCC cannot exceed 20,000 units in any 24-hour period because of risk of thrombosis (unrelated to emicizumab).

Drug Acquisition Costs

We derived net prices from average sales prices (ASP) for the BPAs to calculate treatment-related health care costs, as we did not have data on net prices that included discounts/rebates for these agents.[29] For emicizumab, we did not identify anticipated discounts from WAC to estimate a net

price for the therapy, nor was an ASP available at the time of this analysis.[30] We therefore conducted the base-case analysis using WAC for emicizumab, recognizing that this cost approach disadvantages the emicizumab prophylaxis strategy. Based on the regimen dosage specified in Table 4.4 and available formulations for each drug, the model utilized the lowest-cost combination of tablets/vials for each regimen.

Table 4.6. Drug Cost Inputs

	Emicizumab	rFVIIa	aPCC
Cost Unit	1.5 mg	1 mcg	1 IU
WAC per Unit[30]	$148.80	$2.16	$2.16
ASP per Unit[29]	N/A	$2.00	$1.94
ASP Discount from WAC	N/A	7%	10%

ASP: average sales price, WAC: wholesale acquisition cost
WAC as of November 6th, 2017

Health Care Utilization Costs

Additional healthcare utilization could occur with treatment administration and during therapy, including the initial office visit where patients are taught how to self-administer, hospitalizations for treatment of bleeds, and visits to hemophilia treatment centers (Table 4.7). Costs for supportive care other than the treatment of a bleed event were derived from published studies and included costs of ongoing care that are essential to the current paradigm of treatment.

Table 4.7. Health Care Utilization Costs

	Emicizumab and BPA Prophylaxis	No Prophylaxis
Per-bleed non-pharmacy costs*† (weekly)[31]		
Age 6-18 years‡	$747	$3,081
Age 19-44 years	$4,490	$4,490
Age > 45 years	$6,689	$6,689
Arthropathy surgery cost†[32]	$45,286	

BPA: bypassing agent
*Non-pharmacy cost includes outpatient visits, hospitalizations, and ER visits.
†Inflated to 2017 US dollars.
‡Only patients age 6-18 years showed a statistically-significant difference in non-pharmacy cost; we modeled this difference before inflating to 2017 US dollars and assumed costs for patients age ≥ 19 years were equivalent.

Adverse Events

Serious treatment-related adverse events, as documented in the trials, were included in the model. Each treatment-related adverse event was assigned an associated cost that was applied for each patient experiencing such an event (Table 4.8).

Costs for serious adverse events were based on resource utilization associated with appropriate adverse event treatments as reported in previous analyses and unit prices from the Centers for Medicare and Medicaid Services (CMS) Medicare Physician Fee Schedule for fiscal year 2017.[33]

Table 4.8. Included Treatment-Related Adverse Events

SAEs	AE Cost[33]	Emicizumab Prophylaxis[13]	No Prophylaxis[13]	BPA Prophylaxis
Skin Necrosis	$7,667	3%	0%	0%
Thrombophlebitis Superficial	$7,708	3%	0%	0%
Thrombotic Microangiopathy	$13,335	3%	0%	0%

AE: adverse event, BPA: bypassing agent, SAE: serious adverse event

Societal Costs and Productivity Losses

We performed a societal perspective analysis to examine the economic burden of hemophilia A with inhibitors, accounting for indirect costs due to the substantial productivity loss experienced by both patients and caregivers. This was estimated by applying derived indirect costs/week for prophylaxis (emicizumab and BPA) and no prophylaxis comparators. Our indirect cost estimates were based on the burden of disease analysis by Zhou et al., which focused on the direct and indirect costs of hemophilia care in the US.[93] The study reported all outcomes in 2011 US dollars, which were inflated to 2017 dollars.

In the Zhou et al. study, a total of 329 participants (164 adults and 165 children) ages 2-64 years were recruited from six HTCs in different regions of the country; 222 were ultimately included and follow-up visits were conducted for an average of 12 months.[93] One hundred forty-six (66%) of included patients had severe hemophilia A (defined as spontaneous bleeding into joints, muscles, and other soft tissues). However, only eight of these patients (3.6%) had inhibitors, and while severe patients' indirect costs were reported separately for those on prophylaxis and not on prophylaxis, only the total indirect cost was presented for the inhibitor patients.

Therefore, we used the annual disaggregated indirect costs for patients receiving prophylaxis and not receiving prophylaxis who had severe hemophilia A and the annual total indirect cost for patients with inhibitors to derive separate annual costs for patients with inhibitors on prophylaxis and not on prophylaxis. First, we assumed the proportion of patients with inhibitors receiving

prophylaxis was the same as that for severe patients. Then we calculated a weighted indirect cost for severe patients based on the proportions on prophylaxis (63%) and not on prophylaxis (37%; weighted annual cost = $11,877) as well as a ratio comparing it to the annual total cost for patients with inhibitors ($21,325; ratio = 1.8). The 2011 total compensation per hour for civilian workers used by Zhou et al. was $30.11; to adjust for inflation, the equivalent estimate for the year 2017 is $35.64.[94] The derived prophylaxis (emicizumab and BPA) and no prophylaxis indirect costs per week were $361 and $690, respectively (for detailed calculation see Appendix F). The higher indirect costs for on demand treatment are due to the larger number of bleeding events.[93]

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 for each input described in the model inputs section above. Probabilistic sensitivity analyses were also performed by jointly varying all model parameters over 5,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results. We used log-normal distributions for bleed rates and rate ratios, adverse event rates, and cost parameters; we used beta distributions for utility parameters and adherence rates.

Additionally, we performed a threshold analysis by systematically altering the price of emicizumab to estimate the maximum prices that would correspond to given willingness-to-pay (WTP) thresholds ranging from $50,000 to $500,000 per QALY.

Scenario Analyses

Multiple scenario analyses were conducted to evaluate the impact of key model choices and assumptions on the robustness of the results and conclusions, including:

- Age at model entry;
- Reduced mortality resulting from lower ABR;
- Higher bleed rates in patients with arthropathy;
- Proportion of patients able to use aPCC on demand when treated with emicizumab; and
- When patients reach the age of 12 years, their bleeding reduction persists at the childhood (i.e., < 12 years) level.

Finally, in response to stakeholder comments, we modeled a scenario making simultaneous assumptions that were favorable to BPAs and unfavorable to emicizumab where we assumed that the reduction in treated bleeds with emicizumab was equivalent to the reduction seen in HAVEN 1 for all bleeds. This "BPA-favoring scenario" analysis (available in Appendix Tables F8-9) made additional imbalanced assumptions to address the following concerns:

- Clinicians may decide it is necessary to only treat bleeds for patients on emicizumab prophylaxis with rFVIIa, which is more expensive than aPCC. In the BPA-favoring scenario, we assume all bleeds on emicizumab are treated with rFVIIa and all bleeds for patients on aPCC prophylaxis are treated with aPCC.
- Adherence to BPA prophylaxis is unlikely to be 100%. We do not have adherence data on emicizumab, while adherence in Antunes et al.[18] was 88%. For the BPA-favoring scenario (as well as the base case), we assume emicizumab lifetime adherence to be 100% and aPCC lifetime adherence to be 88% (thereby reducing costs of aPCC). This assumption is only applied to cost in the model, as we assume the efficacy data mostly reflects trial-reported adherence.
- Clinicians and/or payers may decide that prophylactic therapy is best treated with aPCC. In the BPA-favoring scenario, all prophylaxis in the BPA prophylaxis comparator is aPCC.
- The disutility associated with a bleed event may not impact a patient during the entire week spent in a bleed health state. In the BPA-favoring scenario, we limited the disutility of a bleed event to two days and assumed the full utility for "No Bleed" (vs. the base case's use of an average of bleed and no bleed utilities) would be applied for the remaining five days of each weekly model cycle.
- Adverse events are the same as in the base case. Despite treating bleeding events on emicizumab only with rFVIIa, we continue to assume the rate of thrombotic microangiopathy and thrombotic events that was seen in HAVEN 1.

Model Validation

We used several approaches to validate the model. First, we provided preliminary methods and results to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we refined data inputs used in the model. Second, we varied model input parameters to evaluate face validity of changes in results. We performed model verification for model calculations using internal reviewers. Finally, we compared results to other cost-effectiveness models in this therapy area.

4.3 Results

Base-Case Results

Health System Perspective

Emicizumab prophylaxis resulted in fewer bleed events, equal life years, increased QALYs, and lower costs compared to both no prophylaxis and BPA prophylaxis (Table 4.9). For patients age 12 years or older, emicizumab prophylaxis was estimated to avoid a total of 606 bleeds over a lifetime compared to no prophylaxis and 114 compared to BPA prophylaxis, while QALYs gained were 0.91 and 0.20 versus no prophylaxis and BPA prophylaxis, respectively. For patients under the age of 12 years, the expected reduction in bleeds over a lifetime was 1,091 compared to no prophylaxis and 217 compared to BPA prophylaxis, with respective QALY gains of 2.39 and 0.38. Lifetime incremental costs of emicizumab prophylaxis were approximately $8.9 million lower compared to no prophylaxis and $71 million lower compared to BPA prophylaxis for patients age 12 years or over. For a patient population starting the model under 12 years of age, the lifetime incremental costs of emicizumab were $10 million lower compared to no prophylaxis and $78.5 million lower for emicizumab versus BPA prophylaxis (Table 4.10).

The base case incremental cost-effectiveness ratios for emicizumab are negative, indicating that emicizumab is expected to save costs and increase QALYs by reducing bleeds (with no impact on life years gained because we assumed the same mortality for each comparator in the base case).

Table 4.9. Health System Perspective Results for Emicizumab Prophylaxis Compared to BPA Prophylaxis and No Prophylaxis

Treatment	Prophylaxis Drug Cost	Cost of On-Demand Treated Bleeds	Total Cost	Total Bleed Events (All)	Life Years	QALYs
Patients ≥ 12 Years of Age						
Emicizumab Prophylaxis	$14,952,461	$3,817,130	$19,221,932	107	21.28	15.41
BPA Prophylaxis	$81,418,150	$7,907,405	$90,182,398	221	21.28	15.21
No Prophylaxis	--	$25,525,761	$28,135,154	713	21.28	14.50
Patients < 12 Years of Age						
Emicizumab Prophylaxis	$16,461,362	$3,904,537	$20,683,787	176	28.06	22.79
BPA Prophylaxis	$89,865,693	$8,731,838	$99,212,053	392	28.06	22.41
No Prophylaxis	--	$28,187,098	$31,012,935	1267	28.06	20.40

BPA: bypassing agent, QALY: quality-adjusted life year

Table 4.10. Health System Perspective Incremental Results

Treatment	Incremental Cost	Incremental Bleeds Avoided	Incremental QALYs Gained	Incremental Life Years Gained
Patients ≥ 12 Years of Age				
Emicizumab vs. No Prophylaxis	-$8,913,222	606	0.91	0
Emicizumab vs. BPA	-$70,960,466	114	0.20	0
Incremental C-E Ratio	--	**Less Costly, More Effective**	**Less Costly, More Effective**	**Less Costly, Equally Effective**
Patients < 12 Years of Age				
Emicizumab vs. No Prophylaxis	-$10,000,971	1091	2.39	0
Emicizumab vs. BPA	-$78,528,265	217	0.38	0
Incremental C-E Ratio	--	**Less Costly, More Effective**	**Less Costly, More Effective**	**Less Costly, Equally Effective**

BPA: bypassing agent, C-E: cost-effectiveness, QALY: quality-adjusted life year

Societal Perspective

QALYs and life years in the societal perspective analysis were the same as in the results for the healthcare perspective, thus only the updated indirect and total costs are presented below (Table 4.11). The inclusion of indirect costs had little impact on model results (Table 4.12). Patients receiving no prophylaxis had greater indirect costs compared to indirect costs in patients receiving prophylaxis. Emicizumab prophylaxis remained cost-saving versus no prophylaxis and BPA prophylaxis, and this result was robust to variation in sensitivity analyses.

Table 4.11. Societal Perspective Results for Emicizumab Prophylaxis Compared to BPA Prophylaxis and No Prophylaxis

Treatment	Indirect Cost	Total Cost
Patients ≥ 12 Years of Age		
Emicizumab Prophylaxis	$400,983	$19,623,275
BPA Prophylaxis	$400,983	$90,583,742
No Prophylaxis	$766,602	$28,901,756
Patients < 12 Years of Age		
Emicizumab Prophylaxis	$528,743	$21,212,892
BPA Prophylaxis	$528,743	$99,741,157
No Prophylaxis	$1,010,856	$31,695,614

BPA: bypassing agent

Table 4.12. Societal Perspective Incremental Results

Treatment	Incremental Indirect Cost	Incremental Total Cost
Patients ≥ 12 Years of Age		
Emicizumab vs. No Prophylaxis	-$365,619	-$9,278,481
Emicizumab vs. BPA	$0	-$70,960,466
Incremental C-E Ratio	--	**Less Costly, More Effective**
Patients < 12 Years of Age		
Emicizumab vs. No Prophylaxis	-$482,112	-$10,482,722
Emicizumab vs. BPA	$0	-$78,528,265
Incremental C-E Ratio	--	**Less Costly, More Effective**

BPA: bypassing agent, C-E: cost-effectiveness, QALY: quality-adjusted life year

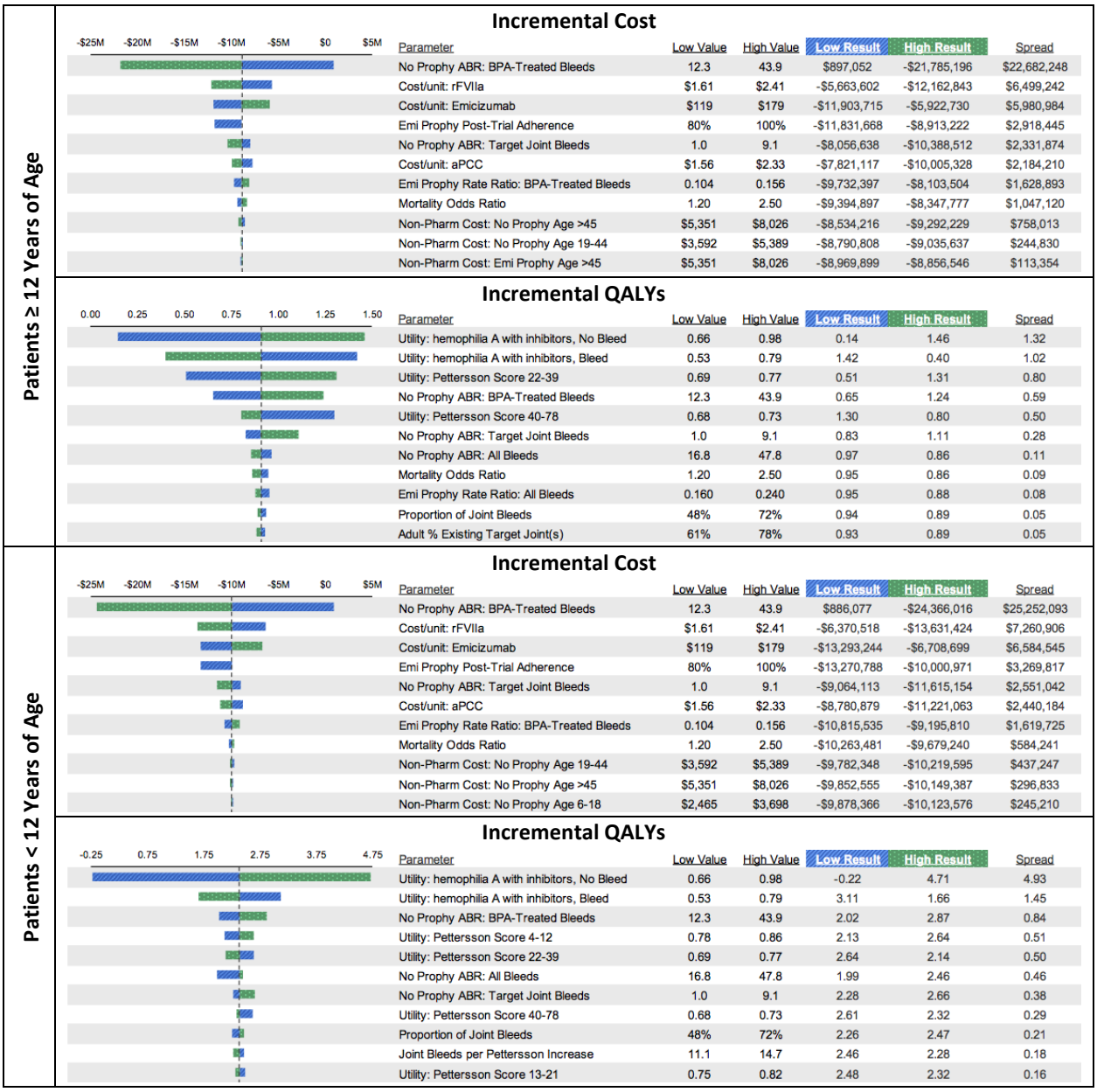
Sensitivity Analysis Results

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e. standard errors) or reasonable ranges to evaluate the impact of changes in drug costs, resource utilization, and treatment effectiveness on incremental cost and incremental QALYs.

When comparing emicizumab prophylaxis to no prophylaxis (Figure 4.2), incremental cost was primarily driven by the HAVEN 1 ABRs for BPA-treated bleeds in the no-prophylaxis group; this parameter was important for deriving transition probabilities for bleed event health states in all three modeled comparators. Other parameters impacting incremental cost included the costs of emicizumab and BPAs, emicizumab adherence (assumed to be 100% in the base case), and other bleed-related parameters. The cost-saving result for emicizumab prophylaxis versus no prophylaxis was robust to nearly all changes in individual model parameters; the sole exception was the lower bound of the estimate of the rate of BPA-treated bleeds in children not receiving prophylaxis.

Incremental QALYs gained for emicizumab versus no prophylaxis were similarly robust to changes in model parameters (Figure 4.2). The primary drivers were utility values for the "No Bleed" and "Bleed" health states, followed by Pettersson score-associated utilities and the ABR for BPA-treated bleeds for no prophylaxis patients. Emicizumab prophylaxis did result in lower QALYs than no prophylaxis, but only when the utility for the "No Bleed" health state was lowered to an extreme of 0.66 (equivalent to the "Bleed" utility) in children, which effectively nullified the modeled lifetime difference between the "No Bleed" and "Bleed" health states.

Figure 4.2. Tornado Diagrams for One-Way Sensitivity Analyses of Emicizumab Prophylaxis Versus No Prophylaxis, for Incremental Costs and Incremental QALYs

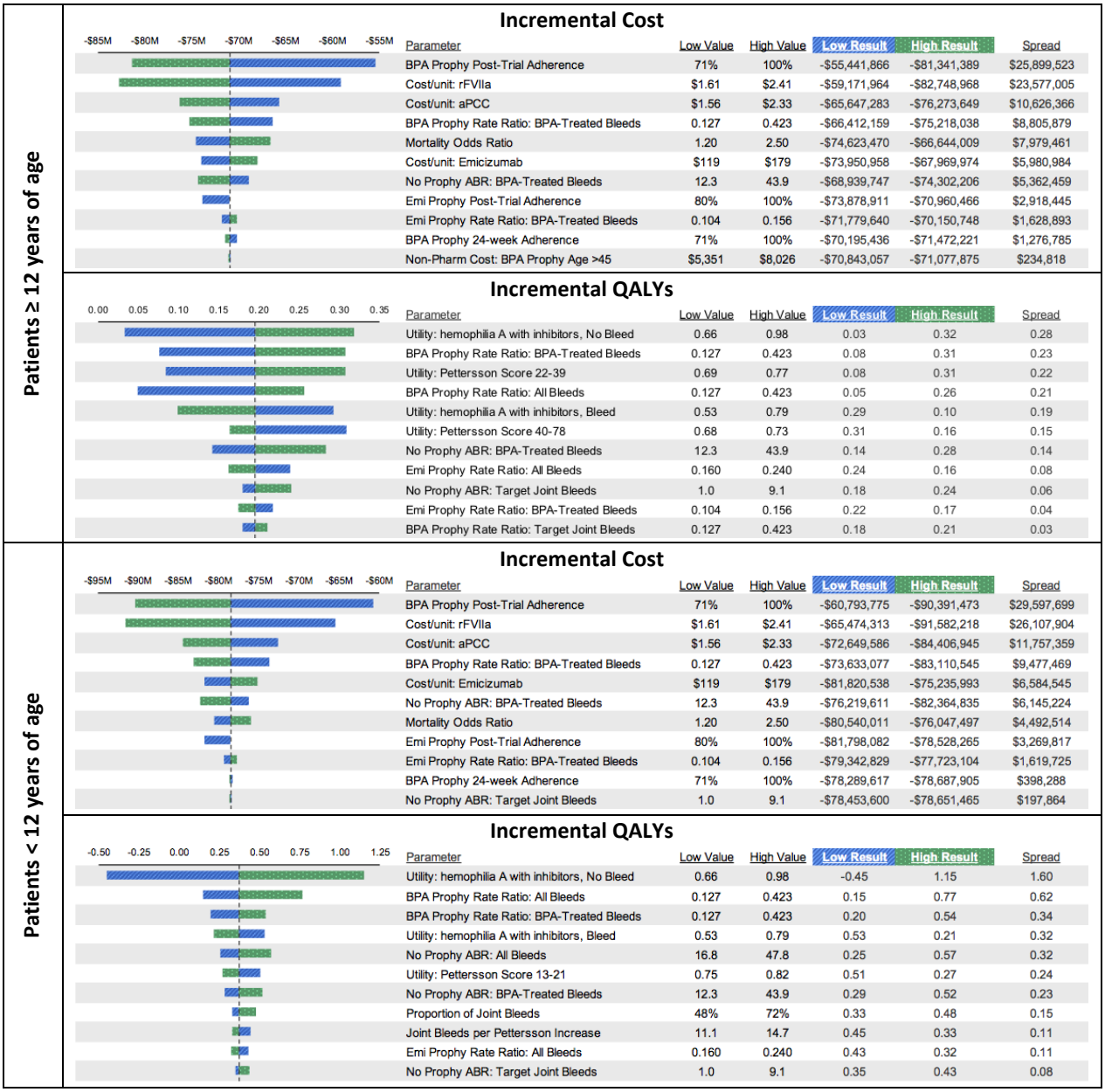


ABR: annualized bleeding rate, BPA: bypassing agent, Prophy: prophylaxis, QALY: quality-adjusted life year

When comparing emicizumab prophylaxis to BPA prophylaxis, incremental cost was primarily driven by BPA prophylaxis adherence, followed by rFVIIa and aPCC costs (Figure 4.3). Other parameters impacting incremental cost included treated bleed rate parameters, the inhibitor patient mortality odds ratio, and the cost of emicizumab. As in the comparison versus no prophylaxis, the cost-saving result for emicizumab prophylaxis versus BPA prophylaxis was robust to changes in individual model parameters. Finally, incremental QALYs gained for emicizumab versus BPA prophylaxis were also robust to changes in model parameters, except for when the "No Bleed" utility was lowered to an

extreme value of 0.66 for children. The primary drivers were utilities and the BPA-treated bleed parameters.

Figure 4.3. Tornado Diagrams for One-Way Sensitivity Analyses of Emicizumab Prophylaxis Versus BPA Prophylaxis, for Incremental Costs and Incremental QALYs



Patients ≥ 12 years of age — Incremental Cost

Parameter	Low Value	High Value	Low Result	High Result	Spread
BPA Prophy Post-Trial Adherence	71%	100%	-$55,441,866	-$81,341,389	$25,899,523
Cost/unit: rFVIIa	$1.61	$2.41	-$59,171,964	-$82,748,968	$23,577,005
Cost/unit: aPCC	$1.56	$2.33	-$65,647,283	-$76,273,649	$10,626,366
BPA Prophy Rate Ratio: BPA-Treated Bleeds	0.127	0.423	-$66,412,159	-$75,218,038	$8,805,879
Mortality Odds Ratio	1.20	2.50	-$74,623,470	-$66,644,009	$7,979,461
Cost/unit: Emicizumab	$119	$179	-$73,950,958	-$67,969,974	$5,980,984
No Prophy ABR: BPA-Treated Bleeds	12.3	43.9	-$68,939,747	-$74,302,206	$5,362,459
Emi Prophy Post-Trial Adherence	80%	100%	-$73,878,911	-$70,960,466	$2,918,445
Emi Prophy Rate Ratio: BPA-Treated Bleeds	0.104	0.156	-$71,779,640	-$70,150,748	$1,628,893
BPA Prophy 24-week Adherence	71%	100%	-$70,195,436	-$71,472,221	$1,276,785
Non-Pharm Cost: BPA Prophy Age >45	$5,351	$8,026	-$70,843,057	-$71,077,875	$234,818

Patients ≥ 12 years of age — Incremental QALYs

Parameter	Low Value	High Value	Low Result	High Result	Spread
Utility: hemophilia A with inhibitors, No Bleed	0.66	0.98	0.03	0.32	0.28
BPA Prophy Rate Ratio: BPA-Treated Bleeds	0.127	0.423	0.08	0.31	0.23
Utility: Pettersson Score 22-39	0.69	0.77	0.08	0.31	0.22
BPA Prophy Rate Ratio: All Bleeds	0.127	0.423	0.05	0.26	0.21
Utility: hemophilia A with inhibitors, Bleed	0.53	0.79	0.29	0.10	0.19
Utility: Pettersson Score 40-78	0.68	0.73	0.31	0.16	0.15
No Prophy ABR: BPA-Treated Bleeds	12.3	43.9	0.14	0.28	0.14
Emi Prophy Rate Ratio: All Bleeds	0.160	0.240	0.24	0.16	0.08
No Prophy ABR: Target Joint Bleeds	1.0	9.1	0.18	0.24	0.06
Emi Prophy Rate Ratio: BPA-Treated Bleeds	0.104	0.156	0.22	0.17	0.04
BPA Prophy Rate Ratio: Target Joint Bleeds	0.127	0.423	0.18	0.21	0.03

Patients < 12 years of age — Incremental Cost

Parameter	Low Value	High Value	Low Result	High Result	Spread
BPA Prophy Post-Trial Adherence	71%	100%	-$60,793,775	-$90,391,473	$29,597,699
Cost/unit: rFVIIa	$1.61	$2.41	-$65,474,313	-$91,582,218	$26,107,904
Cost/unit: aPCC	$1.56	$2.33	-$72,649,586	-$84,406,945	$11,757,359
BPA Prophy Rate Ratio: BPA-Treated Bleeds	0.127	0.423	-$73,633,077	-$83,110,545	$9,477,469
Cost/unit: Emicizumab	$119	$179	-$81,820,538	-$75,235,993	$6,584,545
No Prophy ABR: BPA-Treated Bleeds	12.3	43.9	-$76,219,611	-$82,364,835	$6,145,224
Mortality Odds Ratio	1.20	2.50	-$80,540,011	-$76,047,497	$4,492,514
Emi Prophy Post-Trial Adherence	80%	100%	-$81,798,082	-$78,528,265	$3,269,817
Emi Prophy Rate Ratio: BPA-Treated Bleeds	0.104	0.156	-$79,342,829	-$77,723,104	$1,619,725
BPA Prophy 24-week Adherence	71%	100%	-$78,289,617	-$78,687,905	$398,288
No Prophy ABR: Target Joint Bleeds	1.0	9.1	-$78,453,600	-$78,651,465	$197,864

Patients < 12 years of age — Incremental QALYs

Parameter	Low Value	High Value	Low Result	High Result	Spread
Utility: hemophilia A with inhibitors, No Bleed	0.66	0.98	-0.45	1.15	1.60
BPA Prophy Rate Ratio: All Bleeds	0.127	0.423	0.15	0.77	0.62
BPA Prophy Rate Ratio: BPA-Treated Bleeds	0.127	0.423	0.20	0.54	0.34
Utility: hemophilia A with inhibitors, Bleed	0.53	0.79	0.53	0.21	0.32
No Prophy ABR: All Bleeds	16.8	47.8	0.25	0.57	0.32
Utility: Pettersson Score 13-21	0.75	0.82	0.51	0.27	0.24
No Prophy ABR: BPA-Treated Bleeds	12.3	43.9	0.29	0.52	0.23
Proportion of Joint Bleeds	48%	72%	0.33	0.48	0.15
Joint Bleeds per Pettersson Increase	11.1	14.7	0.45	0.33	0.11
Emi Prophy Rate Ratio: All Bleeds	0.160	0.240	0.43	0.32	0.11
No Prophy ABR: Target Joint Bleeds	1.0	9.1	0.35	0.43	0.08

ABR: annualized bleeding rate, BPA: bypassing agent, Prophy: prophylaxis, QALY: quality-adjusted life year

Probabilistic sensitivity analysis, in which we simultaneously varied all modeled parameters over 5,000 simulations, indicated that emicizumab was cost-effective in 100% of simulations when compared to BPA prophylaxis at all ages, and in approximately 96% and 93% of simulations versus

no prophylaxis in patients ≥ 12 and < 12 years of age, respectively (Table 4.13). Detailed results of the probabilistic sensitivity analysis can be found in Appendix Figures F1-F2.

Table 4.13. Probabilistic Sensitivity Analysis Results: Emicizumab Prophylaxis Versus BPA Prophylaxis and No Prophylaxis

	Proportion of Simulations That Were…					
	Cost-Saving*	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 in Patients ≥ 12 Years of Age						
vs. BPA Prophylaxis	96.8%	100%	100%	100%	100%	100%
vs. No Prophylaxis	91.0%	96.1%	96.2%	96.3%	96.3%	96.3%
Emicizumab in Patients < 12 Years of Age						
vs. BPA Prophylaxis	80.7%	100%	100%	100%	100%	100%
vs. No Prophylaxis	85.9%	92.7%	92.8%	93.1%	93.5%	93.7%

BPA: bypassing agent, QALY: quality-adjusted life year

*Increased QALYs and decreased cost vs. the comparator

Scenario Analysis Results

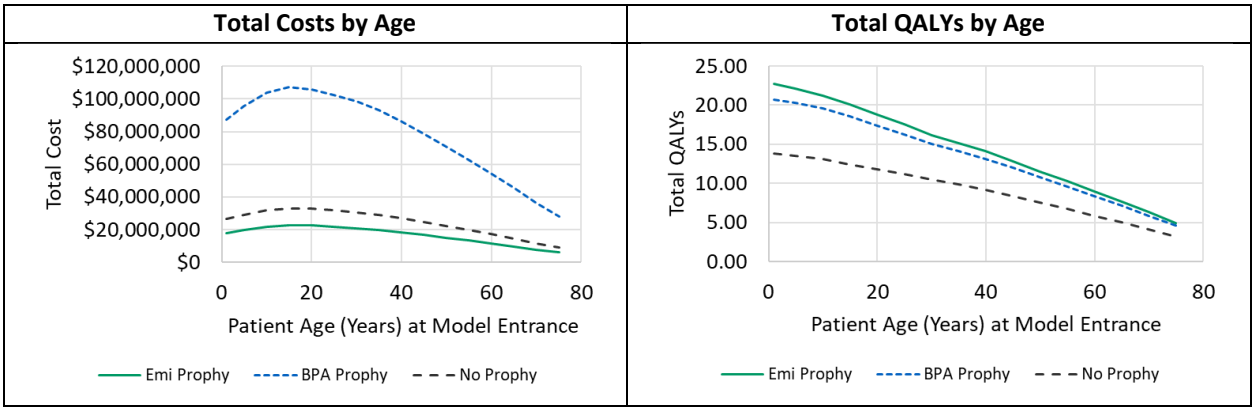
Scenario: Patient Age at Model Entry

The model utilizes a lifetime perspective to estimate costs and health outcomes. Thus, the age at which a patient enters the model has important impacts on the length of time a patient remains in the model to accrue outcomes and costs. An additional dimension to consider is that patient weight increases with age until adulthood (see Appendix Table F10), which increases the required dosages of prophylactic and on-demand treatment with BPAs up to the age at which weight stabilizes. We explored the impacts of age at model entry over a range from age 0 to 75 years.

For all three comparators, total cost increased with age of entry (as weight increased) up to approximately age 18 years; patient weight began to stabilize at approximately age 20 years. As age of entry continued to increase, however, the number of years a patient spent in the model decreased, which offset the increased cost due to increasing weight. Once patient weight stabilized, total cost decreased with increasing age at model entry due to fewer years left to accrue treatment costs. Another important factor is the effect of discounting over time; for example, higher drug costs incurred as an adult (due to increased weight) for a patient who enters the model as a child are greatly discounted, while the same costs for an adult entering the model are not. Regardless, at each age at model entry, emicizumab prophylaxis cost less than the BPA prophylaxis and no prophylaxis comparators.

Age at model entry impacted QALYs gained as expected, showing a decrease with fewer years spent in the model. At each age at model entry, emicizumab prophylaxis resulted in more QALYs gained compared to BPA prophylaxis and no prophylaxis.

Figure 4.4. Total Costs and QALYs by Age at Model Entry



BPA: bypassing agent, Emi: emicizumab, Prophy: prophylaxis

Scenario: Reduced Mortality Resulting from Lower ABR

We implemented a scenario in which patients treated prophylactically with emicizumab or BPAs had the same mortality as hemophilia A patients without inhibitors. We present the results (Table 4.14) based on two approaches: 1) no additional mortality risk compared to US background mortality for both prophylaxis comparators;[91] and 2) an average of inhibitor patient mortality risk[7] and US background mortality for both prophylaxis comparators. In both approaches, no change was made to the no prophylaxis comparator's mortality.

For the first approach, setting prophylaxis patient mortality equal to US background mortality resulted in increased life years compared to no prophylaxis and improved incremental QALYs, but also increased cost compared to no prophylaxis due primarily to more patients being alive to continue prophylaxis. The second approach, using an average of increased inhibitor risk-adjusted mortality and US background mortality, showed similar but less impactful changes to results, as expected. In both cases, emicizumab prophylaxis remained cost-saving versus BPA prophylaxis and no prophylaxis.

Table 4.14. Results of Scenario Analyses Modeling Reduced Mortality in Target Population

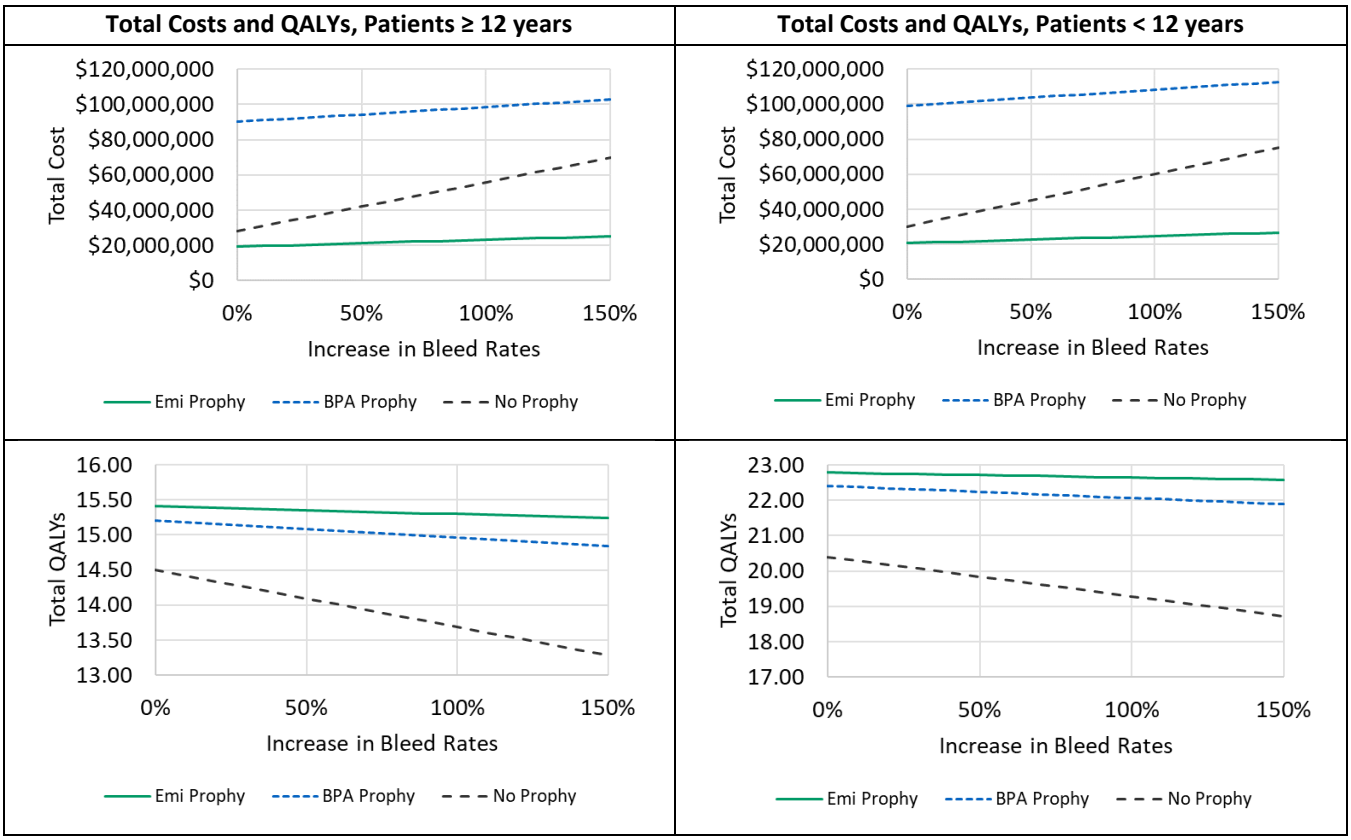
	Emicizumab Prophylaxis			BPA Prophylaxis		
	Cost	QALYs	Life Years	Cost	QALYs	Life Years
Patients ≥ 12 Years of Age						
Base-Case Mortality[7,91]	$19,221,932	15.4	21.3	$90,182,398	15.2	21.3
Averaged Mortality Difference	$19,899,902	16.0	22.1	$93,367,096	15.8	22.1
No Mortality Difference	$20,701,004	16.6	23.0	$97,129,677	16.4	23.0
Patients < 12 Years of Age						
Base-Case Mortality[7,91]	$20,683,787	22.8	28.1	$99,212,053	22.4	28.1
Averaged Mortality Difference	$21,056,722	23.1	28.5	$100,970,582	22.7	28.5
No Mortality Difference	$21,484,213	23.5	29.0	$102,985,967	23.1	29.0

BPA: bypassing agent, QALY: quality-adjusted life year

Scenario: Higher Bleed Rates in Patients with Arthropathy

Multiple stakeholders indicated that bleed incidence tends to increase, particularly for target joints, as bleeds accrue over time. In this scenario we increased bleed rates for patients with target joints/arthropathy across a range of values, from no increase (base case) to 150%. We made the same assumption of bleed increases for all three comparators, so that the only difference among comparators was the baseline ABRs for each. Across a range of bleed rate increases, emicizumab prophylaxis remained the least expensive and resulted in the greatest number of QALYs gained (Figure 4.5).

Figure 4.5. Total Costs and QALYs for Scenario Analyses Modeling Higher Bleed Rates in Patients with Arthropathy



BPA: bypassing agent, Emi: emicizumab, Prophy: prophylaxis, QALY: quality-adjusted life year

Scenario: Proportion of Patients Able to Use aPCC on Demand When Treated with Emicizumab

On-demand treatment with aPCC is less expensive than with rFVIIa. We varied the emicizumab prophylaxis proportion of patients who are treated with aPCC from 0% to 100%, with the remainder of patients receiving rFVIIa for on-demand treatment at each proportion. This scenario only impacted the cost of on-demand treatment for bleeding events.

At 0% of patients receiving aPCC for bleeds, the on-demand treatment cost for patients ages 12 years and over was approximately $5.09 million and the total cost was approximately $20.78 million. At 100% of patients receiving aPCC for bleeds, the on-demand treatment cost was approximately $2.19 million, and the total cost was $17.88 million. Across this range of proportions, emicizumab prophylaxis remained cost-saving versus the other two comparators.

At 0% of patients receiving aPCC for bleeds, the on-demand treatment cost for patients under the age of 12 years was approximately $5.20 million and the total cost was $22.07 million. At 100% of patients receiving aPCC for bleeds, the on-demand treatment cost was approximately $2.24 million

and the total cost $19.11 million. Across this range of proportions, emicizumab prophylaxis remained cost-saving versus the other two comparators.

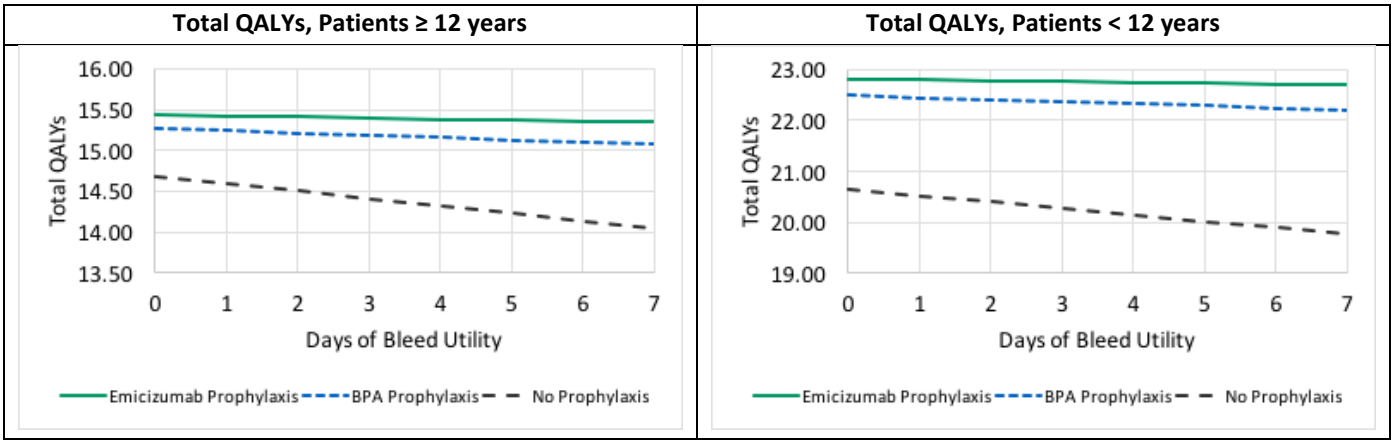
Scenario: Childhood Bleeding Reduction on Emicizumab Prophylaxis Persists into Adulthood

In this scenario, we assumed that the childhood reduction in bleed rates conferred by emicizumab prophylaxis would persist into adulthood. We present results for 37-year old males with bleed reduction rates from HAVEN 2 instead of HAVEN 1. Compared to the base case, emicizumab prophylaxis costs were reduced by approximately $4.18 million, and QALYs were increased by 0.23 when using the HAVEN 2 efficacy estimates for adults.

Scenario: Duration of Bleed Event Utilities

Bleed duration likely varies depending on severity of the bleed, time to treatment, and other variables including bleed location. In this scenario, we varied the number of days that bleed utilities are applied per cycle, while still assuming (as in the base case) the utility for the remaining days in the week was an average of the bleed utility and the utility for no bleed. Therefore, overall QALYs decreased the longer the bleed event utilities were applied. An increase from zero to seven days of bleed event utility resulted in a modest decrease in QALYs for the prophylaxis arms, and a more pronounced effect in the no prophylaxis comparator due to the greater number of bleed events.

Figure 4.6. Total QALYs for Scenario Analyses Modeling Duration of Bleed Utilities



BPA: bypassing agent, Emi: emicizumab, Prophy: prophylaxis, QALY: quality-adjusted life year

Scenario: Analyses Favoring BPA

Results of our BPA-favoring scenario analysis are presented in Appendix Tables F8-9. Expected cost savings of emicizumab prophylaxis were reduced by approximately 50% under these extreme assumptions relative to the base case, but emicizumab remained less costly and more effective than either BPA prophylaxis or no prophylaxis in patients age < 12 and ≥ 12 years respectively.

Threshold Analyses Results

The unit prices at which emicizumab would cross cost-effectiveness thresholds ranging from $50,000 to $500,000 per QALY gained are presented below. Although emicizumab is cost-saving across a range of sensitivity and scenario analyses, the incremental cost over a lifetime horizon is volatile, with ± 20% variation of emicizumab price resulting in an approximately $10 million range of incremental cost saved (see one-way sensitivity analyses above). When the unit price of emicizumab was increased so that it was no longer cost-saving, further small increases in the emicizumab price resulted in relatively large impacts on the incremental cost-effectiveness ratio. We also note that these findings are specific to patients with inhibitors only, as the cost and QALY impacts in less severe patients are likely to be more modest.

Table 4.15. Threshold Analysis Results for Patient Population Age 12 Years and Older

	WAC per Unit (1.5mg)	Unit Price No Longer Cost-Saving	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	Unit Price to Achieve $300,000 per QALY	Unit Price to Achieve $500,000 per QALY
Emicizumab vs. BPA Prophylaxis	$148.80	$854.97	$858.09	$858.19	$858.28	$858.38	$858.57	$858.96
Emicizumab vs. No Prophylaxis	$148.80	$237.50	$254.01	$254.46	$254.91	$255.37	$256.27	$258.08

BPA: bypassing agent, QALY: quality-adjusted life year

Table 4.16. Threshold Analysis Results for Patient Population under 12 Years of Age

	WAC per Unit (1.5mg)	Unit Price No Longer Cost-Saving	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	Unit Price to Achieve $300,000 per QALY	Unit Price to Achieve $500,000 per QALY
Emicizumab vs. BPA Prophylaxis	$148.80	$858.64	$860.26	$860.43	$860.60	$860.77	$861.12	$861.80
Emicizumab vs. No Prophylaxis	$148.80	$239.20	$242.47	$243.56	$244.64	$245.72	$247.88	$252.21

BPA: bypassing agent, QALY: quality-adjusted life year

Model Validation

All mathematical functions in the model were consistent with the report (and supplemental Appendix materials). The model produced findings consistent with expectations when testing individual functions. Sensitivity analyses with null input values ensured the model was producing findings consistent with expectations. Further, independent modelers[a] tested the mathematical functions in the model, as well as specific inputs and corresponding outputs.

Model validation was also conducted in terms of comparisons to other model findings. We found no published economic evaluation comparing emicizumab prophylaxis to BPA prophylaxis or no prophylaxis in the literature. BPAs for both on-demand treatment and prophylaxis in hemophilia A patients with inhibitors have been in use for several years, during which time treatment protocols and more importantly costs of treatment have significantly changed. Therefore, our review of prior economic evaluations only included recent analyses that are similar to our economic evaluation in target population and interventions assessed.

One manufacturer-sponsored study by Earnshaw et al. (2015) compared on-demand treatment with rFVIIa or prophylaxis with aPCC three times per week to a high-dose ITI regimen of 200 IU/kg daily of factor VIII concentrate.[32] The model was structured as a decision tree in which individuals enter as infants with newly-diagnosed (i.e., previously untreated) severe hemophilia A. As in our model, Earnshaw et al. followed patients over lifetime and the average weight of US males over time was used to longitudinally adjust weight-based drug dosing. Also, as in our model, patients experienced bleed rates that were consistent with published clinical trial evidence, and, patients may eventually require orthopedic surgery due to the cumulative effect of bleed events. The study population mimicked those in the International Immune Tolerance Study by Hay and DiMichele, with average population age being less than eight years, while in our model, the younger target population (children) had an average age of seven years.[95] Both models follow Fischer et al.'s approach of assuming that only patients with a Pettersson score of 28 or more required orthopedic joint surgery.[90] Generally, the direction of costs and effects reported in the Earnshaw model is the same as in the ICER model, with BPA prophylaxis generating fewer bleeds and more QALYs at higher cost than no prophylaxis.

The Earnshaw model projects 1,828 and 718 bleeding events for on-demand treatment and BPA prophylaxis treatment, respectively. Setting the starting age to one year in the ICER model (to more closely resemble the start age in the Earnshaw model), we projected a total number of 1,477 and 762 bleeds over lifetime for no prophylaxis and BPA prophylaxis, respectively. While the estimates

[a] Randall Curtis, MBA, Co-Investigator, Patient Reported Outcomes, Burdens, and Experiences (PROBE) study; Declan Noone, Msc, MEng, BEng, Health Economist, HCD Economics; Jamie O'Hara, MS, Director of Strategy, HCD Economics

of projected bleeds with BPA prophylaxis treatments are similar, the difference in the no prophylaxis treatment may partly be explained by the on-demand drugs modelled (rFVIIa and aPCC in the ICER model and rFVIIa only in the Earnshaw model), as well as differences in the underlying data used by Earnshaw that indicate an 82% reduction in the number of bleeding events on BPA prophylaxis versus on-demand treatment, whereas in the ICER model a 72% reduction is applied. The projected difference in bleeds is indeed 10% larger in the Earnshaw model compared to the ICER model. Further, the Earnshaw model reports similar discounted QALYs for BPA prophylaxis as our model for patients under the age of 12 years (i.e., 21 in the Earnshaw model vs. 22 in the ICER model). Earnshaw et al. estimated QALYs in the on-demand strategy that were lower than the ICER estimate for the no prophylaxis strategy (15 vs. 20), which is consistent with the relatively higher number of bleeds projected in the Earnshaw model. The lifetime cost estimates of the ICER model (i.e., $32 million for no prophylaxis treatment and $102 million for BPA prophylaxis) are higher than those from the Earnshaw model ($22 million and $43 million, respectively), mostly due to differences in drug costs which are 1.2 to 2 times higher in the ICER model. There are certain key differences between the two models. First, Earnshaw et al. calculated the on-demand BPA dosage for rFVIIa at 105 mcg/kg every two to three hours while the ICER model calculated this based on a weighted average of average total units/kg administered per bleed (rFVIIa, aPCC, and dual therapy estimates were provided) as observed in the HAVEN-1 trial. Furthermore, our model applied a combined, weighted dose of both BPAs for both on-demand treatment and prophylaxis, while Earnshaw et al. limited on-demand treatment to rFVIIa only and prophylaxis to aPCC only. Second, BPA costs used in our model are higher than those used by Earnshaw et al. (rFVIIa $2 vs. $1.53 per mcg; aPCC $1.94 vs. $1.55 per IU). Our model also used a higher utility value for patients on inhibitors relative to the utility awarded by Earnshaw et al. (0.82 vs. 0.79). Finally, while our model categorizes utility based on whether bleeding was into a target joint, as well as awards a disutility for treatment events such as an orthopedic surgery and administering a central venous access line, it is unclear whether Earnshaw et al. used similar assumptions.

To compare the annual costs of patients receiving BPA as on-demand treatment as reported by Guh et al., we ran the ICER model for a population with an initial age of seven years to resemble the Guh population of patients receiving BPAs.[12] In doing so, the ICER model projects an annual total cost estimate of $1.1 million in the no prophylaxis treatment strategy, of which $1 million (90%) are annual drug costs. Guh et al. report similar cost estimates (considering their 2008 price year) of $0.8 million in total annual costs, of which $0.7 million (~89%) are annual drug costs.

A model by Farrugia et al. compares the long-term cost-effectiveness of prophylaxis versus on-demand therapy with BPAs in patients with severe hemophilia A.[96] Patients entering this model did not have inhibitors, but did have a probability of developing inhibitors to clotting factor concentrates. Patients with inhibitors were treated with ITI. The model was built from both a US payer perspective as well as a UK National Health Service (NHS) perspective. We report the US-specific model inputs and outcomes as most relevant to our comparison. While results in the two

models cannot be compared with each other due to differences in initial target population as well as treatment pathways for patients with inhibitors, certain methodologies and cost inputs have been reviewed for comparison. Farrugia et al. modeled annual cycles while the ICER model uses weekly cycles in keeping with the multitude of clinical event probabilities in severe hemophilia A patients. While the ICER model awards a utility of 0.82 to inhibitor patients with no active bleed, Farrugia et al. awarded a utility of 0.67 to the same patient cohorts, irrespective of on-demand treatment or prophylaxis with BPAs. Farrugia et al. also model a higher baseline ABR compared to the ICER model. The ICER model uses a higher dosage for on-demand treatment (based on HAVEN-1 observed total units/kg) while Farrugia et al. used a dosage of 1,800 IU/kg with aPCC, although the duration of bleed event was not specified. The costs of rFVIIa per mcg were lower in the Farrugia et al. model compared to those in the ICER model ($0.95 vs. $2.00) while cost of aPCC was higher than in the ICER model ($2.17 vs. $1.94 per IU).

We reviewed other economic models,[97-100] but have not compared them due to differences in target population, geographic setting, and interventions.

4.4 Summary and Comment

Our analysis indicates that emicizumab prophylaxis compared to no prophylaxis and BPA prophylaxis in hemophilia A patients with inhibitors would be cost-saving. Emicizumab was estimated to be more effective and to generate more QALYs at lower total cost, both from a health system and societal perspective, compared to no prophylaxis and to BPA prophylaxis (assuming a 7% and 10% discount on list prices of rFVIIa and aPCC, respectively). This finding remained robust over a wide range of sensitivity and scenario analyses. These included analyses of patient age at model entry, reduced mortality, higher bleed rates in patients with target joints, proportion of patients able to use aPCC on demand when treated with emicizumab, and assuming persistence of childhood bleeding reduction into adulthood. While emicizumab remained cost-saving and more effective in nearly all sensitivity analyses, the results were most sensitive to uncertainty in ABRs for BPA-treated bleeds for no prophylaxis patients, utility values for “No Bleed” and “Bleed” health states, BPA prophylaxis adherence, and rFVIIa and aPCC costs.

Limitations

In the absence of long term data on the development of arthropathy by treatment strategy, the probability of developing arthropathy is modeled based on the cumulative number of joint bleeds and the associated Pettersson Score. The modeled prophylaxis adherence is based on clinical trial data and is likely higher than real world adherence; this overestimates the expected costs as well as the effectiveness of prophylaxis strategies, though not necessarily to the same extent. Modeled lifetime outcomes are highly dependent on the short-term outcomes observed in the HAVEN 1, HAVEN 2 and PROOF clinical trials, and the emicizumab outcomes versus no prophylaxis for patients < 12 years old are derived using results of a single-arm trial.

Note that the results of this economic evaluation are applicable to a specific population (i.e., those with hemophilia A with inhibitors to factor VIII who will not be treated with ITI or for whom ITI has been unsuccessful), and not to the broader population of patients with hemophilia A who do not have inhibitors.

Conclusions

In conclusion, the findings of our analysis suggest that emicizumab prophylaxis provides gains in quality-adjusted life years at substantially lower costs over a lifetime horizon, with these findings remaining robust across multiple sensitivity and scenario analyses.

5. Additional Considerations

Our reviews seek to provide information on 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. 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 emicizumab to BPA prophylaxis.

Table 5.1. Potential Other Benefits or Contextual Considerations (Not Specific to Any Disease or Therapy)

Potential Other Benefits
This intervention provides significant direct patient health benefits that are not adequately captured by the QALY.
This intervention offers reduced complexity that will significantly improve patient outcomes.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.
This intervention will significantly reduce caregiver or broader family burden.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients who have failed other available treatments.
This intervention will have a significant impact on improving return to work and/or overall productivity.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.
This intervention will have a significant positive impact outside the family, including on schools and/or communities.
This intervention will have a significant impact on the entire "infrastructure" of care, including effects on screening for affected patients, on the sensitization of clinicians, and on the dissemination of understanding about the condition, that may revolutionize how patients are cared for in many ways that extend beyond the treatment itself.
Potential Other Contextual Considerations
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
This intervention is the first to offer any improvement for patients with this condition.
Compared to "the comparator," there is significant uncertainty about the long-term risk of serious side effects of this intervention.
Compared to "the comparator," there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.

5.1 Other Benefits

Emicizumab has a number of "other benefits" under the ICER value framework as modified for ultra-rare conditions.

- The availability of a subcutaneous therapy administered weekly (when compared with an intravenous therapy that must be administered many times per week) touches on several issues addressed in the framework:
    - The treatment is less burdensome and has reduced complexity, which is likely to improve adherence as well as the ability for some patients with limited mobility to self-administer prophylaxis; intravenous administration has been identified as a barrier to starting and adhering to prophylaxis[14].
    - Caregivers will find administering therapy much less burdensome and time consuming, and, in young children, will not need to deal with techniques required to reduce the risks of infection and thrombosis in central venous access devices (ports).
    - Such a therapy will facilitate work decisions, including pursuing employment that requires travel, or a more active lifestyle where previously patients may have been unable or unwilling to engage in such jobs/careers. Additionally, there may be health benefits to patients from greater ability to engage in physical activities.
- Having a more effective therapy should also enhance career and education choices, and additionally should reduce burdens on caregivers, families, schools, and communities by potentially allowing children to participate in activities from which they would previously have been restricted.
- Emicizumab offers a novel mechanism of action, and so is likely to benefit patients who did not achieve adequate prophylaxis with BPAs.

5.2 Contextual Considerations

There are a number of contextual considerations relevant to patients with hemophilia A with inhibitors and to treatment with emicizumab:

- Hemophilia creates substantial burdens that affect quality of life and can also affect length of life.
- Hemophilia is a disease that affects patients for their entire lives.
- There are important uncertainties about the risks of thrombosis in patients treated with emicizumab, particularly when situations occur that might alter coagulation or the need for coagulation, such as sepsis, head trauma, major trauma, and central lines.
- 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.

6. Value-Based Price Benchmarks

Value-based price benchmarks were not calculated for emicizumab in this population, as treatment at the current price is cost-saving and provided additional benefit compared with no prophylaxis or BPA prophylaxis for patients with hemophilia A and inhibitors to factor VIII. We note that this judgment of the value-base price benchmark applies only to the currently-indicated population, and would not necessarily apply to other, broader populations potentially covered by expanded indications.

7. Potential Budget Impact

7.1 Overview

We used the results from the cost-effectiveness model to estimate the potential total budgetary impact of emicizumab in hemophilia A patients with inhibitors in the United States. We used the WAC for each drug in our estimates of budget impact. Since results from our cost-effectiveness analysis show emicizumab to be a dominant strategy (i.e., higher total QALYs and lower total costs relative to comparators), and we currently do not know the level of discount from WAC for emicizumab, and emicizumab at WAC pricing is cost-saving in our budget impact analysis, we did not model its budget impact at a discounted WAC or at commonly cited cost-effectiveness threshold prices.

7.2 Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential cost of using each new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over one- and five-year time horizons. The five-year timeframe was of primary interest given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of patients treated with the new therapy.

The potential budget impact analysis included two candidate populations eligible for treatment: hemophilia A patients with inhibitors less than 12 years of age and 12 years of age or older. To estimate the size of the potential candidate populations for treatment, we first identified the total number of hemophilia patients in the US: 20,000 in 2016.[35] Based on data published in a 2016 report by the WFH, hemophilia A patients comprise 77% of all hemophilia patients in the US.[34] From this report we estimated the prevalence of hemophilia A at 0.005% and the prevalence of those with inhibitors among hemophilia A patients at 6%. The WFH report also estimated that 97% of all hemophilia A patients are male and 34% of all hemophilia A patients are under 13 years of age. Applying these proportions to the projected US population from 2018 to 2022[36] resulted in estimates of 634 eligible patients aged 12 years and older and 327 eligible patients under 12 years of age. Among these eligible patients, we assumed a 20% uptake each year over five years.

ICER's methods for estimating potential budget impact are described in detail elsewhere and have recently been updated. The intent of our revised approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy.

Briefly, we evaluate a new drug that would take market share from one or more drugs and calculate the budget impact associated with displacing use of existing therapies with the new intervention. In this analysis, we assumed that in both populations, emicizumab will replace prophylaxis with BPAs and will also be used in patients who are eligible for but not on prophylaxis. We assumed emicizumab market share would come equally from patients with prophylaxis and no prophylaxis. For each population, the threshold prices of emicizumab differ for each comparator: BPA prophylaxis or no prophylaxis. We also used a 50:50 ratio while calculating emicizumab's undiscounted health care costs at each of the threshold prices, taking equally from its costs versus each comparator.

Using this approach to estimate potential budget impact, we then compared our estimates to a budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility. As described in ICER's methods presentation (http://icer-review.org/wp-content/uploads/2016/02/ICER-Value-Assessment-Proposed-Updates-Webinar-021317.pdf), this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug approvals by the FDA over the most recent two-year period, and the contribution of spending on retail and facility-based drugs to total health care spending. Calculations are performed as shown in Table 7.1.

For 2017-18, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $915 million per year for new drugs.

Table 7.1. Calculation of Potential Budget Impact Threshold

Item	Parameter	Estimate	Source
1	Growth in US GDP, 2017 (est.) +1%	3.20%	World Bank, 2016
2	Total health care spending, 2016 ($)	$2.71 trillion	CMS NHE, 2014
3	Contribution of drug spending to total health care spending (%)	17.7%	CMS National Health Expenditures (NHE), 2016; Altarum Institute, 2014
4	Contribution of drug spending to total health care spending ($) (Row 2 x Row 3)	$479 billion	Calculation
5	Annual threshold for net health care cost growth for ALL new drugs (Row 1 x Row 4)	$15.3 billion	Calculation
6	Average annual number of new molecular entity approvals, 2015-2016	33.5	FDA, 2017
7	Annual threshold for average cost growth per individual new molecular entity (Row 5 ÷ Row 6)	$457.5 million	Calculation
8	Annual threshold for estimated potential budget impact for each individual new molecular entity (doubling of Row 7)	$915 million	Calculation

7.3 Results

Table 7.2 illustrates the per-patient budget impact calculations based on unit WAC ($148.80) for emicizumab compared to a 50:50 mix of prophylaxis with BPAs and no prophylaxis in hemophilia A patients with inhibitors. In patients aged 12 years and older, emicizumab at WAC pricing would reduce the budget by approximately $1.85 million per patient annually. In patients under 12 years of age, emicizumab at WAC pricing would reduce the budget by approximately $720,000 per patient annually. The annual budget impact of emicizumab for the entire eligible cohort of patients results in cost-savings of approximately $706 million and $146 million in the ≥12 years and <12 years populations, respectively.

Table 7.2. Per-Patient Budget Impact Calculations Over a Five-year Time Horizon for Eligible Patient Populations, using Emicizumab WAC

	Average Annual Per Patient Budget Impact	
	≥ 12 years old	< 12 years old
Emicizumab Prophylaxis	$974,560	$265,618
Prophylaxis with BPA + No Prophylaxis[†]	$2,827,256	$985,416
Difference	-$1,852,696*	-$719,798*

*Cost-saving

[†]In a 50:50 ratio

As stated in earlier sections of this report, the results of this analysis are applicable to a specific population (i.e., those with hemophilia A with inhibitors to factor VIII who will not be treated with ITI or for whom ITI has been unsuccessful), and not to patients who may be treated with ITI or the broader population of patients with hemophilia A who do not have inhibitors. For that target population, results from our five-year budget impact analysis show that at its current WAC, emicizumab will reduce budgets for hemophilia A treatment across both age categories compared to a market comprising active prophylaxis with BPAs and no prophylaxis.

8. Summary of the Votes and Considerations for Policy

8.1 About the New England CEPAC Process

During New England CEPAC public meetings, the New England CEPAC Panel 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. Panel 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 Panel 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 CEPAC Panel during their deliberation and help to shape recommendations on ways the evidence can apply to policy and practice.

After the CEPAC Panel votes, a policy roundtable discussion is held with the CEPAC Panel, 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 March 29 meeting, the New England CEPAC Panel discussed issues regarding the application of the available evidence to help patients, clinicians, and payers address important questions related to the use of emicizumab for treating patients with Hemophilia A and inhibitors to Factor VIII. Following the evidence presentation and public comments (public comments from the meeting can be accessed here, starting at minute 1:16:00), the CEPAC Panel voted on key questions concerning the comparative clinical effectiveness, and 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.

Given the analysis that demonstrated cost saving of treatment with emicizumab in comparison with bypassing agents, the panel did not vote on any questions related to the long-term value for money. The voting results are presented below, along with specific considerations mentioned by CEPAC Panel members during the voting process.

In its deliberations and votes related to value, the New England CEPAC Panel 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 8.1 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 Panel uses the ICER Evidence Rating Matrix as its conceptual framework for considering comparative clinical effectiveness.

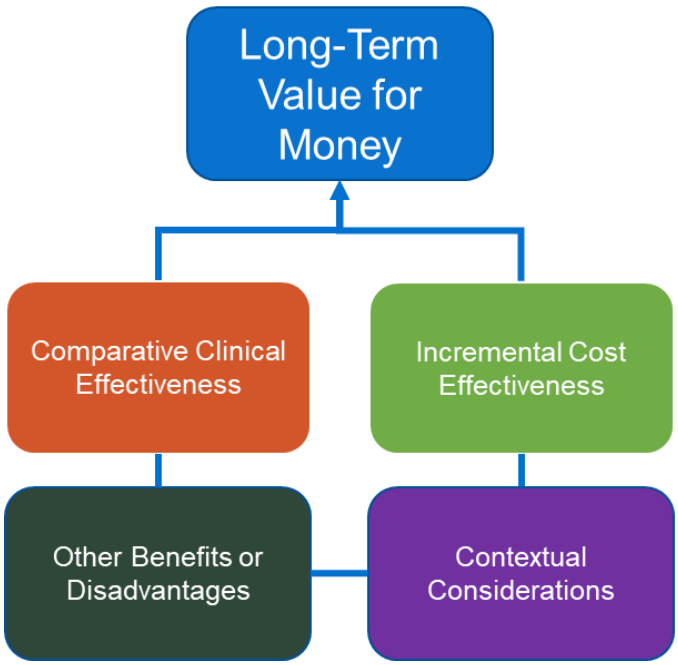
2. Estimated incremental cost-effectiveness is the average incremental cost per patient of one intervention compared to another to achieve a desired "health gain," such as an additional stroke prevented, case of cancer diagnosed, or gain of a year of life. Alternative interventions are compared in terms 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 New England CEPAC 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. 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 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 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 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 8.1. **Conceptual Structure of Long-term Value for Money**



8.2 Voting Results

Patient population for all questions: *Patients with hemophilia A with inhibitors to factor VIII who will not be treated with immune tolerance induction (ITI) or for whom ITI has been unsuccessful. When necessary, age ranges are specified in voting questions.*

1. Is the evidence adequate to demonstrate that prophylactic emicizumab provides a net health benefit compared with no prophylactic therapy?

   For patients < 12 years of age

Yes: 11	No: 2

   For patients ≥ 12 years of age

Yes: 13	No: 0

Comments: For patients over 12 years old, the panel unanimously voted that the evidence from the HAVEN 1 randomized trial was adequate to demonstrate a net health benefit of emicizumab over no prophylaxis. For patients under 12, there was general concern over the lack of peer reviewed evidence. As several panel members noted, preliminary results from HAVEN 2 have only been made available in abstracts, press releases, and conference presentations. Those panel members who voted "no" indicated that the quality of the evidence is not sufficient to demonstrate a net health benefit. The majority of CEPAC members still felt confident in voting "yes" based on inference from the existing evidence, the magnitude of the effect, and input from clinical and patient experts. Clinical experts highlighted the extra effect of beginning emicizumab early in preventing cumulative joint damage, arthropathy, and disability. One panel member further justified his vote, despite the lack of high quality evidence in children under 12, by suggesting that there is no reason to not believe the treatment results would be different for a pediatric population, in which there are no RCTs, than for an adult population, in which there is higher quality evidence. 11 panel members voted that the evidence is sufficient to demonstrate that emicizumab provides a net health benefit in the pediatric population.

2. Is the evidence adequate to demonstrate that prophylactic emicizumab provides net health benefits compared with prophylactic therapy with bypassing agents (BPAs)?

For patients < 12 years of age

Yes: 11	No: 2

For patients ≥ 12 years of age

Yes: 13	No: 0

Comment: For patients over 12 years old, the panel unanimously voted that the evidence from the HAVEN 1 observational data was adequate to demonstrate a net health benefit of emicizumab over BPA therapy. The panel justified their votes by acknowledging that even with the potential for biases in the observational data, the effect size was significantly large that it could likely not be explained by confounding or bias. For patient under 12 years old, like the concerns discussed above, the panel was concerned about the quality of the evidence, including the lack of peer review, the sample size of the pediatric population, and the lack of randomized data. The discussion turned to ethical considerations in studying

children in a randomized trial, and panel members asked if we should perhaps have a higher tolerance for uncertainty in the evidence given the pediatric population; however, experts allayed concerns by contextualizing how the evidence to support prophylaxis treatment (in patients without inhibitors) came from a pivotal randomized study evaluating the effect of prophylaxis in infants on joint damage. Again, 11 panel members voted that the evidence was sufficient to demonstrate a net health benefit for emicizumab prophylaxis in comparison to BPA prophylaxis.

3. When compared to prophylactic therapy with BPAs, does emicizumab offer one or more of the following "other benefits"? (select all that apply)

# of Votes	Other Benefits
11	This intervention offers reduced complexity that will significantly improve patient outcomes.
3	This intervention will reduce important health disparities across racial, ethnic, gender, socioeconomic, or regional categories.
13	This intervention will significantly reduce caregiver or broader family burden.
9	This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other treatments have failed.
12	This intervention will have a significant impact on improving return to work and/or overall productivity.
9	This intervention will have a significant positive impact outside the family, including on schools and/or communities.
3	This intervention will have a significant impact on the entire "infrastructure" of care, including effects on screening for affected patients, on the sensitization of clinicians, and on the dissemination of understanding about the condition, that may revolutionize how patients are cared for in many ways that extend beyond the treatment itself.
8	There are other important benefits or disadvantages that should have an important role in judgments of the value of this intervention: _____

Comment: Panel members voted that prophylaxis with emicizumab provided many other benefits that are not necessarily captured in the clinical data. There was significant discussion around the impact on caregivers and families. One caregiver said that before her son's inhibitor was controlled with emicizumab, her family was always in crisis mode, with many trips to the emergency room and treatment centers, causing her to miss work, him to miss school, and impacting attention to other family members. Panel members also agreed that a weekly subcutaneous injection provided a significant benefit over existing daily or every-other-day intravenous therapy, especially considering potential complications in venous access for small children and the elderly.

3. Are any of the following contextual consideration important in assessing emicizumab's long-term value for money? (select all that apply)

# of Votes	Contextual Considerations
5	This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
5	This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
0	This intervention is the first to offer any improvement for patients with this condition.
1	Compared to prophylactic therapy with BPAs, there is significant uncertainty about the long-term risk of serious side effects of this intervention.
0	Compared to prophylactic therapy with BPAs, there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.
1	There are additional contextual considerations that should have an important role in judgments of the value of this intervention: _____.

Comment: Panel members recognized the extreme burden of illness on patients, impacting their length of life and quality of life. While emicizumab is an important advance, they acknowledged that bypassing agents do play an important role for patients, especially going forward in treating acute bleeds. Panel members discussed the uncertainty in the safety data that must be monitored over the long term; and one clinical expert expressed concern that treating clinicians might inadequately treat acute bleeds with bypassing agents given concerns over side effects. Clinicians, he worried, might give too large a dose of bypassing agents to treat acute bleeds, increasing risk of severe adverse events; or, alternatively, give insufficient doses of BPAs to treat a bleed, fearing adverse effects. Given that much of treatment happens in home-based care, clinical experts expect a paradigm shift in how to manage acute bleeds in patients on emicizumab in a home-based setting.

While panelists recognize that there are inadequate long-term data to measure durability of response, they discussed the risk tradeoff, and there was consensus that the benefits from emicizumab in health outcomes outweigh the long-term risk for adverse events or waning durability of response. One patient pointed out that even if the efficacy of emicizumab were to wane after 5 or 10 years due to development of antibodies, there would be important quality of life gains for those years.

Finally, considering the historical context of patients with hemophilia, a community of patients who experienced the devastating effects of tainted blood supply in the 1980s; and the contributions of patients with hemophilia to the medical profession –many basic mechanisms of clotting were elucidated by studying hemophilia, and medical students still learn about the clotting cascade through the lens of hemophilia; panel members wanted to give special consideration to the population of patients with hemophilia and recognize the benefit they provided to us all in medicine

8.3 Roundtable Discussion and Key Policy Implications

Following its deliberation on the evidence, the New England CEPAC Panel engaged in a moderated discussion with a policy roundtable about how best to apply the evidence on emicizumab in treating patients with hemophilia A and inhibitors to policy and practice. The policy roundtable members included two patient representatives; two clinical experts; two payers, both public and private; and a representative from each of the drug manufacturers with indications for prophylactic therapy for treating patients with inhibitors. 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 H).

Table 8.1. Policy Roundtable Members

Policy Roundtable	
Susan Begelman, MD Vice President, US Medical Affairs Genentech	**Stephen Pipe, MD** Professor of Pediatrics and Communicable Diseases, Professor of Pathology, University of Michigan
Kathleen Gondek, PHD Global Head of Outcomes Research and Epidemiology, Shire	**Margaret V. Ragni, MD, MPH** Professor of Medicine, Division of Hematology/Oncology, University of Pittsburgh; Director, Hemophilia Center of Western PA
Tom Kowalski, RPH Clinical Pharmacy Director, Blue Cross Blue Shield Massachusetts	**Mark W. Skinner, JD** President and CEO, Institute for Policy Advancement; President, World Federation of Hemophilia USA
Herman Kranc, RPH Manager-Integrated Care Connecticut Department of Social Services	**Sonji Wilkes, BA** Parent & Caregiver of Child with Inhibitors Assoc. Dir of Advocacy, Hemophilia Federation of America

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

1) **Financial toxicity for patients and their families is an important feature of the hemophilia landscape. Although the progress in clinical treatment innovation in the past few years has been welcomed by all, the combination of extraordinarily high prices and an insurance structure that often requires significant cost sharing by patients results in financial toxicity that affects families significantly year after year. Payers, manufacturers, and policy makers need to recognize the seriousness of this problem and seek new approaches to address it.**

   Despite an innovation like emicizumab, which will save hundreds of thousands of dollars per

patient per year for the health system, most patients and families will continue to face financial toxicity as out of pocket maximum cost-sharing expenses will continue to occur within a very short period of time early each year. Needed are lower prices and expanded patient support programs from manufacturers, new mechanisms from insurers to make the economic impact of care predictable and spread over a longer time period, and broader approaches from policymakers to reduce the growth of high deductible insurance plans as a primary method to restrain premium growth. Clinicians can also help by serving as vocal witnesses of the effects of financial toxicity on their patients and take responsibility at the individual and specialty society level for being leaders in identifying the financial toxicity faced by their patients and in pushing all parties in the health system to come up with new solutions.

2) **Innovation that addresses unmet clinical need and produces overall cost savings in the health system is ideal and should be encouraged. However, treatments like emicizumab and the potential cures for hemophilia on the horizon can appear cost saving at a very high price given the huge existing annual costs for many patients with hemophilia. In these situations, reasonable value-based pricing for new treatments requires consideration of a new paradigm for "shared savings" between innovators and society.**

   The ICER economic evaluation deemed that emicizumab is cost saving, especially in the very high cost population of patients with inhibitors. However, emicizumab is considered cost saving because it reduces the need for BPA prophylaxis, which can cost over $80,000 per week per patient. Still, emicizumab is a very expensive intervention, with lifetime costs for treating some patients with prophylaxis reaching over $20 million.

   Is it "fair" for the developers and manufacturers of emicizumab to realize several billion dollars a year in revenue while saving the health system significant amounts as well? Many would say yes and would highlight the importance of substantial rewards being needed to encourage further innovation of this kind. But what if a one-time cure for hemophilia becomes available for this same group of patients who can have $80-90 million lifetime health costs? Should the innovator seek a price that captures most of those downstream savings? It seems clear that pricing at that level would prove unaffordable to health systems in the short term, but a deeper question arises about whether and how the downstream savings should be shared between innovators and society. Given that society has been expending resources for many years to provide extremely high cost therapies to patients who require them, as well as providing funding for research on new therapies, there needs to be consideration of how to reward innovators appropriately while returning considerable savings to the health system, and to society at large. How this concept of "shared savings" should operate in an area like hemophilia will be an important issue for policy discussions that should occur very soon in the U.S. ICER intends to convene leaders from the life science and payer communities to begin discussion of this issue in the near future.

3) **In assessing the value of treatments for hemophilia, payers should be aware of important benefits and contextual considerations that are not typically captured in cost-effectiveness analyses.**

   At the New England CEPAC public meeting, there was near consensus that emicizumab provided patients with inhibitors several other benefits, including reduced complexity of administration, a major impact on caregiver and family burden, improvements in productivity (both for the patient and their caregiver), and a positive impact on schools and/or communities. The CEPAC also recognized several important contextual considerations, including the high severity and lifetime burden of disease for these patients, and the historical context of patients with hemophilia A, especially the catastrophic effects of tainted blood supply in the 1980s which devastated the hemophilia patient community. Payers need to be aware of these other benefits and contextual considerations when assessing treatment value and making coverage determinations.

4) **Despite challenges to conducting randomized trials in small patient populations such as hemophilia A, patients and clinicians should recognize the importance of these trials in developing the rigorous evidence needed to help guide treatment as more treatments and treatment pathway choices emerge.**

   We heard from clinicians and patients that given the historical experiences of the hemophilia patient community, there is some hesitance to participate in randomized trials, and there is also a sense that progress has been made in this small patient population in the absence of RCTs. While this may be true in some circumstances, decisions around the best use of ITI versus emicizumab, and the potential use of emicizumab for prophylaxis in patients without inhibitors will be severely hampered if only observational data are available. Indeed, according to one expert on our roundtable, one landmark randomized study transformed care for patients with hemophilia A by demonstrating the effect of prophylactic treatment on joint damage in infants. High quality randomized evidence will become even more important as additional options for treatment become available for treating patients with hemophilia.

5) **Instead of relying on manufacturers to design trials to evaluate the short-term outcomes of specific agents, specialty societies need to urgently develop a set of prototypical pathways of care around the use of ITI, emicizumab, and other treatments so that future research can offer the opportunity for every patient to enroll in trials of pathways of care that will address the key clinical options available to patients.**

   Research in the area of hemophilia risks following the pattern of much research in oncology, where studies often focus on emerging treatments but fail to evaluate how best to

sequence different treatment options. As treatment options continue to increase in hemophilia, it is incumbent upon specialty societies to lead the way in developing sets of "pathways" of care that represent potentially reasonable approaches to care. These pathways will help drive some consensus around best practice among clinicians, and they will also highlight important opportunities for future research to address questions that are important to clinicians and patients but that might not be prioritized by manufacturers. For example, areas of future research on ITI and emicizumab may include: at what age to initiate ITI; which patients with inhibitors might be managed without ITI; duration of ITI; use of emicizumab to avoid exposure to factor VIII in patients believed to be at high risk for developing inhibitors.

6) **Hemophilia patient organizations are leaders in working with manufacturers and other stakeholders to develop core sets of patient-important outcomes for clinical trials. These organizations should continue to advance their work in this area and can hopefully serve as mentors for other patient groups seeking to catalyze the introduction of more patient-centric outcomes in clinical research.**

   As hemophilia patient communities organized in the aftermath of the blood supply crisis, they became leaders in convening stakeholders to develop patient-relevant outcome measures for clinical trials. As leaders in this field, patient groups in hemophilia should continue to work to ensure that research captures the outcomes that are of greatest importance to patients. This is particularly important because understanding value requires understanding the impacts of therapies on patients and their families.

7) **Given that emicizumab may gain indications for broader use, indication-specific pricing will likely be essential in order to tailor the price to reflect the clinical and economic value of the drug in different patient populations.**

   The price of emicizumab is cost-saving in its current indication/population of patients with inhibitors, given the already extremely high costs of caring for such patients. If emicizumab expands its indication to those without inhibitors, the current price would potentially raise substantial concerns around affordability and access that could be addressed in part through indication specific pricing.

8) **The Centers for Medicare and Medicaid Services (CMS) and private payers should carefully consider the ramifications of a potential switch of coverage of emicizumab within the insurance structure from the medical benefit to the pharmacy benefit.**

   Factor therapies for hemophilia are currently covered as Medicare Part B benefits, and some patients may not have purchased part D coverage. Additionally, under part D, cost sharing with patients is potentially quite different than under part B. Likewise, for patients with commercial insurance, patients are nervous about a restructuring of benefits for

emicizumab based on a potential shift from the medical benefit to the pharmacy benefit, including potential for drug management and differential out-of-pocket co-payments distinct from co-insurance and deductibles under the medical benefit. Payers need to consider the potential impact on patient access in making their ultimate determination.

9) **The patient community should be aware of the potential for relationships with manufacturers to introduce conflicts of interest for them and for clinicians.**

   Manufacturers of therapies for hemophilia have played an important role in teaching patients about care of hemophilia, including educating children about how to administer at-home prophylaxis through specially targeted programming. While important benefits accrue to patients and families from educational activities, the potential for important conflicts of interest should not be overlooked since they may create the potential for favoring certain treatments or may influence dosing and patterns of care for at-home treatment.

10) **State Medicaid programs should carefully evaluate the policy options and experiences of states that have opted for mandates for patients to receive their hemophilia therapies through Hemophilia Treatment Centers (HTCs). These mandates may limit access to some degree but allow the state to reap the advantages of 340 B pricing for all patients. Alternatively, some states have opted to forego a mandate for treatment at HTCs in favor of negotiating their own rebates with manufacturers**.

    Medicaid programs in both Washington and Oregon require that patients obtain blood factor through hemophilia treatment centers in order to procure a 340B rebate.[101] These states have made a financial judgment that the rebate obtained through the Federal 340B program provides savings over the Federal Medicaid rebate plus any supplemental rebates they are able to acquire through individual state Medicaid negotiations. According to experts, states have these two options and it is not entirely clear which option works best for patients and provides the best value for state Medicaid programs. Given the extremely high costs of therapies for hemophilia, states should look at which of these options provides the greatest potential savings.

11) **Given that emicizumab has a novel mechanism of action and that clinical studies have not yet evaluated long-term safety, all stakeholders need to be vigilant regarding new information on longer-term outcomes of patients treated with emicizumab.**

    Like all new therapies, there may be safety issues around emicizumab that have not yet been fully elucidated. The hemophilia community, in particular, has prior experience with therapies that have unanticipated harms and should remember this experience despite the excitement of the potential value that emicizumab brings to patients and families.

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This is the first ICER review of emicizumab for hemophilia A.

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Appendices

Appendix A. Search Strategies and Results

Table A1. PRISMA 2009 Checklist

	#	Checklist item
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.
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., I^2) 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., healthcare 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 of Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to Present and Cochrane Central Register of Controlled trials

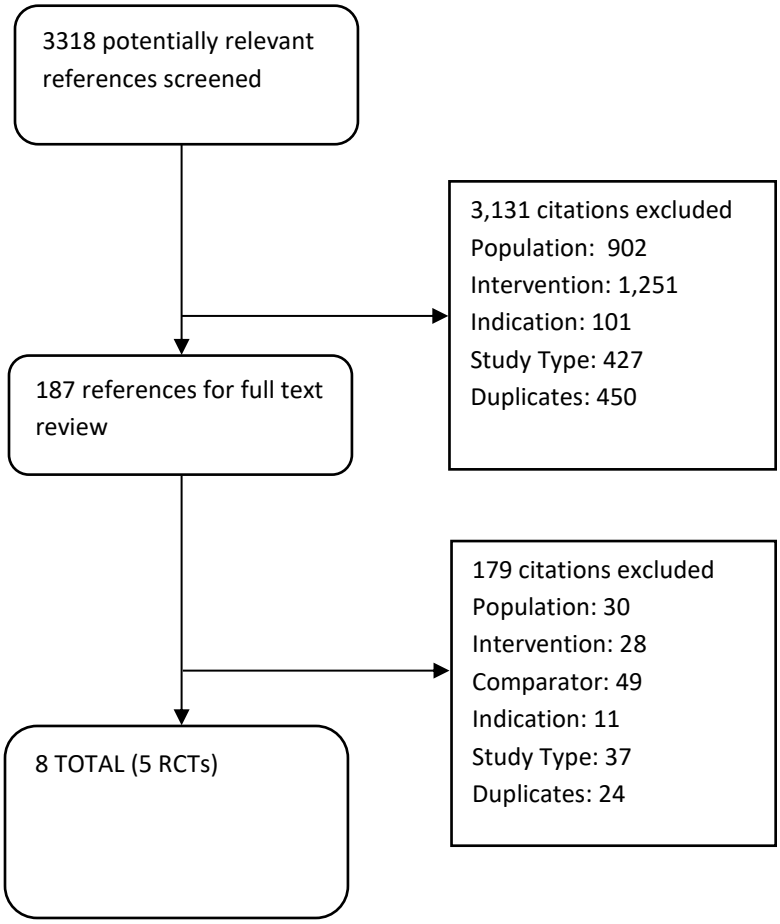
No.	Search Terms	Results
1	h?emophilia A/	20198
2	h?emophilia A.mp.	22139
3	(h?emophilia adj5 factor 8).mp.	24
4	(h?emophilia adj5 factor viii).mp.	4609
5	1 or 2 or 3 or 4	22223
6	h?emophilia/	20198
7	h?emophilia.mp	26528
8	5 or 6 or 7	26528
9	h?emophilia B/	4258
10	h?emophilia B.mp.	5226
11	(h?emophilia adj5 factor 9).mp.	3
12	(h?emophilia adj5 factor ix).mp.	955
13	9 or 10 or 11 or 12	5294
14	13 not (5 and 13)	2240
15	8 not 14	24288
16	Blood Coagulation Factors/	13997
17	aPCC.mp.	241
18	activated PCC.mp.	42
19	activated prothrombin complex concentrate$.mp	385
20	feiba.mp.	397
21	Autoplex.mp.	33
22	anti-inhibitor coagulant complex.mp	44
23	(recombinant adj3 (factor VII$ or fvii$ or f7$ or factor 7$)).mp.	5203
24	rFVII$ or rF7$).mp	2292
25	NovoSeven.mp.	500
26	bypass$ agent$.mp.	360
27	prophylaxis.mp.	117051
28	16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27	135580
29	15 and 28	4861
30	emicizumab.mp.	23
31	ACE910.mp	29
32	29 or 30 or 31	4877
33	(abstract or addresses or autobiography or bibliography or biography or clinical trial, phase i or case report or comment or congresses or consensus development conference or duplicate publication or editorial or guideline or in vitro or interview or lecture or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or personal narratives or portraits or practice guideline or review or video-audio media).pt.	4659902
34	cohort studies/ or longitudinal studies/ or prospective studies/ or retrospective studies/ or comparative study.pt.	3284891
35	control groups/ or (control* adj2 (clinical or group* or trial* or study or studies or design* or arm*)).ti,ab. or ("clinical trial" 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").pt. or (random?ed adj6 (study or trial* or (clinical adj2 trial*))).ti,ab. or ((single or doubl*) adj2 blind*).ti,ab.	2301977
36	34 or 35	4859733
37	32 not 33	3321
38	36 and 37	982

39	(animals not (humans and animals)).sh.	4643837
40	38 not 39	969
41	limit 40 to English language	922
42	Remove duplicates from 41	789

Table A3. Embase Search Strategy

No.	Search Terms	Results
#1	'hemophilia a'/exp OR 'haemophilia a'/exp	20,017
#2	'hemophilia a' OR 'haemophilia a'	21,711
#3	(hemophilia OR haemophilia) NEAR/5 ('factor viii' OR 'fviii' OR 'factor 8')	5,458
#4	#1 OR #2 OR #3	22,458
#5	'hemophilia'/exp OR 'haemophilia'/exp	37,322
#6	'hemophilia' OR 'haemophilia'	44,163
#7	#4 OR #5 OR #6	44,163
#8	'hemophilia b'/exp OR 'haemophilia b'/exp	6,918
#9	'hemophilia b' OR 'haemophilia b'	7,586
#10	(hemophilia OR haemophilia) NEAR/5 ('factor ix' OR 'fix' OR 'factor 9')	1,912
#11	#8 OR #9 OR #10	7,819
#12	#11 NOT (#4 AND #11)	3,399
#13	#7 NOT #12	43,924
#14	'apcc' OR 'activated pcc' OR 'activated prothrombin complex concentrate*' OR 'feiba' OR 'autoplex' OR 'anti-inhibitor coagulant complex'	1,947
#15	recombinant NEAR/3 ('factor vii*' OR fvii* OR f7a OR 'factor 7a')	9,657
#16	rfvii* OR rf7* OR novoseven	5,273
#17	'bypass* agent*'	829
#18	'prophylaxis'	203,387
#19	#14 OR #15 OR #16 OR #17 OR #18	213,240
#20	#13 AND #19	9,302
#21	emicizumab	56
#22	ace910	53
#23	#20 OR #21 OR #22	9,349
#24	#23 AND ('chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)	1,771
#25	#23 NOT #24	7,578
#26	'animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp	25,231,833
#27	'human'/exp	18,673,163
#28	#26 AND #27	18,673,163
#29	#26 NOT #28	6,558,670
#30	#25 NOT #29	7,268
#31	#30 AND [english]/lim	6,993
#32	#31 AND [medline]/lim	2,703
#33	#31 NOT #32	3,999
#34	'randomized controlled trial'/exp OR 'controlled clinical trial'/exp OR random*:ti,ab OR placebo:ti,ab OR 'drug therapy':lnk OR trial:ti,ab OR groups:ti,ab	6,529,548
#35	'clinical article'/exp OR 'controlled study'/exp OR 'major clinical study'/exp OR 'prospective study'/exp OR 'cohort analysis'/exp OR 'cohort':ti,ab OR 'compar*':ti,ab OR 'groups':ti,ab OR 'case control':ti,ab OR 'multivariate':ti,ab	12,639,901
#36	#34 OR #35	13,912,700
#37	#33 AND #36	2,529

Figure A1. PRISMA Flow Chart Showing Results of Literature Search for Hemophilia A



Appendix B. Coverage Policies

Figure B1. Example of Harvard Pilgrim's Coverage Policy of FEIBA.

CVS/caremark™

SPECIALTY GUIDELINE MANAGEMENT

FEIBA (anti-inhibitor coagulant complex [human])

POLICY A. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met, and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication

- Hemophilia A and hemophilia B with inhibitors

Compendial Use

- Acquired hemophilia A

All other indications are considered experimental/investigational and are not a covered benefit.

B. REQUIRED DOCUMENTATION

The following information is necessary to initiate the prior authorization review:

- ☐ Laboratory documentation of highest Bethesda titer in members with hemophilia A or hemophilia B with inhibitors

C. CRITERIA FOR APPROVAL

1. Hemophilia A with Inhibitors

Authorization for 12 months may be granted to members who are prescribed FEIBA for hemophilia A with inhibitors (see Appendix) when the inhibitor titer is ≥ 5 Bethesda units per milliliter (BU/mL).

2. Hemophilia B with Inhibitors

Authorization for 12 months may be granted to members who are prescribed FEIBA for hemophilia B with inhibitors (see Appendix) when the inhibitor titer is ≥ 5 BU/mL.

3. Acquired Hemophilia A

Authorization for 12 months may be granted for members who are prescribed FEIBA for acquired hemophilia A.

D. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must meet ALL initial authorization criteria.

E. DOSAGE AND ADMINISTRATION

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines.

F. APPENDIX: Inhibitors - Bethesda Units (BU)

The presence of inhibitors is confirmed by a specific blood test called the Bethesda inhibitor assay.

- High-titer inhibitors:
  - ≥ 5 BU/mL
  - Inhibitors act strongly and quickly neutralize factor
- Low-titer inhibitors:
  - < 5 BU/mL
  - Inhibitors act weakly and slowly neutralize factor

REFERENCES

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- *Acquired hemophilia*. World Federation of Hemophilia. http://www1.wfh.org/publications/files/pdf-1186.pdf. Accessed December 21st, 2015.
- Huth-Kuhne A, Baudo F, Collins P, et al. International recommendations on the diagnosis and treatment of patients with acquired hemophilia A. *Haematologica*. 2009;94(4):566-75.
- Franchini M, Mannucci PM. Acquired haemophilia A: a 2013 update. *Thromb Haemost*. 2013;110(6):1114-20.
- National Hemophilia Foundation. MASAC recommendations concerning products licensed for the treatment of hemophilia and other bleeding disorders. Revised August 2015. MASAC Document # 237. Accessed December 21st, 2015.
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- National Hemophilia Foundation. MASAC recommendations regarding prophylaxis with bypassing agents in patients with hemophilia and high titer inhibitors. MASAC Document #220.
- https://www.hemophilia.org/sites/default/files/document/files/masac220.pdf. Accessed December 21, 2015.

Figure B2. Abridged Example of Tufts Health Plan Coverage Policy for Factor Products and Bypassing Agents

TUFTS Health Plan

Pharmacy Medical Necessity Guidelines: Factor Products

Effective: March 14, 2017

Prior Authorization Required	√	Type of Review – Care Management	
Not Covered		Type of Review – Clinical Review	
Pharmacy (RX) or Medical (MED) Benefit	MED	Department to Review	PRECERT /MM

This Pharmacy Medical Necessity Guideline applies to the following: **Tufts Health Plan Commercial Plans** ☒ Tufts Health Plan Commercial Plans – large group plans ☒ Tufts Health Plan Commercial Plans – small group and individual plans **Tufts Health Public Plans** ☒ Tufts Health Direct – Health Connector ☐ Tufts Health Together – A MassHealth Plan ☐ Tufts Health RITogether – A RIte Care + Rhody Health Partners Plan **Tufts Health Freedom Plan products** ☒ Tufts Health Freedom Plan - large group plans ☒ Tufts Health Freedom Plan - small group plans	**Fax Numbers:** All plans except Tufts Health Direct – Health Connector: PRECERT:617.972.9409 Tufts Health Direct – Health Connector only: MM:888.415.9055

Note: For Tufts Health Plan Medicare Preferred Members, please refer to the Tufts Health Plan Medicare Preferred Prior Authorization Criteria. Background, applicable product and disclaimer information can be found on the last page.

OVERVIEW

The plan covers factor products (monoclonal and recombinant) for factor VIII deficiency (classic hemophilia), for factor IX deficiency (Christmas factor deficiency), for factor VII deficiency (extrinsic factor deficiency), for hereditary factor X deficiency, for factor XIII deficiency (also known as fibrin stabilizing factor deficiency), and for von Willebrand disease. The plan also covers recombinant coagulation factor VIIa (NovoSeven®) for acquired hemophilia.

Coagulation Factor VIIa (Recombinant) agent

- NovoSeven® RT

Anti-inhibitor Coagulant Complex (Plasma-derived) agent

- FEIBA NF

COVERAGE GUIDELINES

This policy supersedes **ALL** Factor Products for treatment of Blood Coagulation Disorders Policies prior to September 2001.

Coverage for factor products may be provided by the plan for Members with a diagnosis of hemophilia A, hemophilia B, or von Willebrand disease who meet any one of the criteria described below:

1. Treatment and/or management of acute bleeding in Members with severe hemophilia, and maintenance therapy as needed to maintain trough factor levels at 1% or greater **OR**
2. Treatment and/or management of acute bleeding episodes for Members with mild hemophilia (factor levels > 5% and <30%) or moderate hemophilia (factor levels of 1% - 5%), such as bleeding episodes associated with surgery or trauma **OR**
3. Treatment and/or management of acute bleeding in Members with von Willebrand disease, and in clinical situations in which patients with von Willebrand disease are at increased risk of bleeding (i.e., surgery or trauma)

OR

4. Treatment and/or management of significant menorrhagia in women with von Willebrand disease

Note: There are no widely accepted severity categories for von Willebrand disease as there are for Hemophilia.

NovoSeven® or Novoseven RT (Coagulation Factor VIIa [recombinant])

In addition to the above criteria, the plan may cover NovoSeven® or Novoseven RT (Coagulation Factor VIIa [recombinant]) for Members with acquired hemophilia or congenital factor VII deficiency when either of the following criteria is met:

1. Treatment and/or management of acute bleeding episodes for Members with acquired hemophilia, and in clinical situations in which patients with acquired hemophilia are at increased risk of bleeding (i.e. surgery or trauma)

OR

2. Treatment and/or management of acute bleeding in Members with congenital factor VII deficiency, and in clinical situations in which patients with congenital factor VII deficiency are at increased risk of bleeding (i.e., surgery or trauma)

LIMITATIONS

1. The quantity of factor product dispensed should be a reasonable estimation of a 30-day supply based on the patient's current utilization and packaging restrictions.
   Note: The designated provider will contact a Tufts Health Plan Care Manager when they identify that a Member does not meet the Tufts Health Plan Clinical Criteria, or if the Member has severe disease with an inhibitor titer, frequent bleeding episodes and/or frequency hospitalization, or who may benefit from case management services.

Appendix C. Previous Systematic Reviews and Technology Assessments

Previous Systematic Reviews

We identified two systematic reviews on patients with hemophilia and inhibitors. One systematic review assessed the effects of bypassing agent prophylaxis in people with hemophilia A or B with inhibitors and the other systematic review compared recombinant factor VIIa concentrate with plasma-derived concentrates for treating acute bleeding episodes. Both reviews are summarized below.

Chai-Adisaksopha C, Nevitt SJ, Simpson ML, Janbain M, Konkle BA. Bypassing agent prophylaxis in people with hemophilia A or B with inhibitors (Review). *Cochrane Database of Systematic Reviews*. 2017; (9): 1-3

In this review, Chai-Adisaksopha and colleagues evaluated the effects of prophylaxis with bypassing agent (BPA) to prevent bleeding in patients with hemophilia and inhibitors. The researchers identified four randomized studies, two of which compared activated prothrombin complex concentrate (aPCC) to no prophylaxis, while the other two trials compared different doses of rFVIIa. aPCC was shown to significantly reduce the mean overall bleeding rates (mean difference: -7.27 [95% CI -9.92 to -4.62]), and the mean number of joint bleeds (mean difference: -6.60 [95% CI -9.32 to -3.88]). Meta-analysis results did not establish significant benefit on health-related quality of life with prophylaxis use. High-dose and low-dose rFVIIa prophylaxis were found to similarly reduce overall bleeding rate (mean difference: -0.82 [95% CI -2.27 to 0.63]) and target joint bleeding rate (mean difference: -3.20 [95% CI -7.23 to 0.83]). The authors concluded that prophylaxis with BPAs may be effective in reducing bleeding in patients with hemophilia and inhibitors but noted a need for additional studies in this area.

Matino D, Makris M, Dwan K, D'Amico R, Iorio A. Recombinant factor VIIa concentrate versus plasma-derived concentrates for treating acute bleeding episodes in people with haemophilia and inhibitors (Review). *Cochrane Database of Systematic Reviews*. 2015; (12): 1-3

In this review, Matino and colleagues sought to assess the clinical effectiveness of rFVIIa concentrate compared to plasma-derived concentrates in the treatment of acute bleeding episodes for patients with hemophilia and inhibitors. The reviewers identified 15 trials, of which two trials that compared rFVIIa to aPCC met the inclusion criteria. Both trials had methodological errors, which includes selection and performance bias, attrition bias, and detection bias. Thus, a meta-analysis was not performed. Results from the two trials showed that rFVIIa and aPCC had similar efficacy, were well tolerated by patients, and caused no clotting complications. The authors concluded that both products were similar in efficacy and safety, although, noting a need for additional studies of better quality.

Appendix D. Ongoing Studies

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
rFVIIa					
Study of Recombinant Factor VIIa Fusion Protein (rVIIa-FP, CSL689) for On-demand Treatment of Bleeding Episodes in Patients With Hemophilia A or B With Inhibitors CSL Behring NCT02484638	Phase II and III Open-label Multiple-dose Dose Escalation Non-Randomized Parallel Assignment Estimated Enrollment: 54	1. Experimental: CSL689 low-dose 2. Experimental: CSL689 high-dose 1. Active Comparator: Eptacog alfa low-dose Single injection of low-dose Eptacog alfa in Part 1 for PK evaluation 2. Active Comparator: Eptacog alfa high-dose Single injection of high-dose Eptacog alfa in Part 1 for PK evaluation	Inclusion Criteria • Male subjects with hemophlia A or B and inhibitors • Age ≥ 12 and ≤ 65 years • High responding inhibitor with documented historical inhibitor titer > 5 Bethesda Units/mL Exclusion Criteria • BMI > 30 kg/m² • Advanced atherosclerotic disease • Recognized history of thromboembolic events, including deep vein thrombosis • HIV-positive subjects who have low cluster of differentiation 4 (CD4)+ lymphocyte count (200/mcL or less) at screening	Primary Outcome Measures • Incremental recovery • Elimination half-life • Treatment success with first CSL689 injection • Total clearance Secondary Outcome Measures • Number of bleeding events requiring > 1 CSL689 injection • Number of CSL689 injections per bleeding event • Treatment success at population best dose • Proportion of recurrences • Proportion of bleeding events with ultrarapid progression • Number of subjects with TEAEs • Number of subjects with an antibody response	October 25, 2019

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
A Phase III Study on the Safety, Pharmacokinetics and Efficacy of Coagulation Factor VIIa (PERSEPT2) LFB USA, Inc. NCT02448680	Phase III Randomized Crossover Assignment Open Label Estimated Enrollment: 24	1. Biological: Coagulation rFVIIa A cross over design to assess the efficacy of 2 separate dose regimens (75 mcg/kg and 225 mcg/kg) of Coagulation Factor VIIa (Recombinant) for the treatment of bleeding episodes in hemophilia A or B patients with inhibitors to Factor VIII or Factor IX	Inclusion Criteria • Male with hemophilia A or B of any severity • Positive inhibitor test BU ≥5 • Experienced >=3 bleeding episodes of any severity in the past 6 months • Age: Birth to <12 years old • Parents or legal guardians must be capable of understanding and be willing to comply with the conditions of the protocol Exclusion Criteria • Be immunosuppressed (patient may not be receiving systemic immunosuppressive medication) • Allergic or hypersensitive to rabbits • Platelet count <100,000/mL • Undergone any major surgical procedure within 1 month prior to first administration of study drug	Primary Outcome Measures • Bleeding episode treatment success Secondary Outcome Measures • Time to bleeding success • Immunogenicity assessment • Pharmacokinetic profile assessment based on plasma concentrations of rfVIIa	June 30, 2017

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Emicizumab					
A Study to Evaluate the Safety and Tolerability of Prophylactic Emicizumab in Hemophilia A Patients With Inhibitors (STASEY) Hoffmann-La Roche NCT03191799	Phase III Single-Arm Open Label Multicenter Estimated Enrollment: 200	1. Emicizumab: Initial dosing will be 3 mg/kg/week subcutaneously for 4 weeks; Maintenance dosing will follow at 1.5 mg/kg/week subcutaneously for the remainder of the 2-year treatment period.	Inclusion Criteria • Body weight >= 40 kilogram • Documented treatment with BPAs or FVIII concentrates in the last 6 months (on-demand or prophylaxis). • Adequate hematologic, hepatic, and renal function Exclusion Criteria • History of illegitimate drug or alcohol abuse within 12 months prior to screening • Known HIV infection with CD4 count <200 cells/mcL within 6 months prior to screening • Concurrent disease, treatment, or abnormality in clinical laboratory tests that would prevent the participant's safe participation in and completion of the study • Additional conditions that may increase the risk of bleeding or thrombosis	Primary Outcome Measures • Occurrence and severity of AEs including thromboembolic, TMA, systemic hypersensitivity, anaphylaxis, and anaphylactoid events Secondary Outcome Measures • Number of Bleeds Over Time • Haemo-A-QoL Questionnaire Score in Participants >= 18 Years • Haemo-QoL-SF Questionnaire Score in Participants 12-17 Years of Age • EQ-5D-5L Score • EmiPref questionnaire	September 4, 2020

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
A Study of Emicizumab Administered Subcutaneously (SC) in Pediatric Participants With Hemophilia A and Factor VIII (FVIII) Inhibitors (HAVEN 2) Hoffmann-La Roche NCT02795767	Phase III Single-Arm Open Label Multicenter Estimated Enrollment: 80	1. Emicizumab will be administered subcutaneous weekly dose at 3 milligrams per kilogram per week for 4 weeks, followed by 1.5 mg/kg/week up to 52 weeks. From 12 weeks onwards, the dose can be increased from 1.5 to 2.25 mg/kg/week or from 2.25 to 3.0 mg/kg/week if the participant has developed >/=2 bleeds in 12 weeks from Week 5 or 9, respectively.	Inclusion Criteria • Children less than < 12 years of age, with allowance for participants 12-17 years of age who weigh <40 kg and participants <2 years of age • Treatment with BPAs • Adequate hematologic, hepatic, and renal function Exclusion Criteria • Ongoing (or planning to receive during the study) ITI therapy or prophylaxis treatment with FVIII • Previous or current treatment for thromboembolic disease or signs of thromboembolic disease • Known HIV or hepatitis B or C • Use of systemic immunomodulators • Participants at high risk for TMA	Primary Outcome Measures • Number of Bleeds Over Time • Proportion of patients with AE • Ctrough of emicizumab Secondary Outcome Measures • Reduction From Baseline in Number of All Bleeds • Change From Baseline in Activated Partial Thromboplastin Time (aPTT) • Haemo-QoL-SF Questionnaire Score in Participants 12-17 Years of Age • Inhib-QoL Questionnaire Score • EQ-5D-5L Score	April 28, 2018

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
A Study to Evaluate the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Emicizumab Given Every 4 Weeks in Participants With Hemophilia A (HAVEN 4) Hoffmann-La Roche NCT03020160	Phase III Non-Randomized Parallel Assignment Open Label Multicenter Estimated Enrollment: 48	1. Emicizumab: Expansion Part - Participants will receive SC emicizumab at a loading dose of 3 mg/kg every week for initial 4 weeks followed by a maintenance dose of 6 mg/kg every 4 weeks for a minimum of 24 weeks. 2. Emicizumab: PK Run-in Part - Participants will receive SC emicizumab at a dose of 6 mg/kg every 4 weeks for a minimum of 24 weeks.	Inclusion Criteria • Children less than < 12 years of age, with allowance for participants 12-17 years of age who weigh <40 kg and participants <2 years of age criteria are met • Treatment with BPAs • Adequate hematologic, hepatic, and renal function Exclusion Criteria • Ongoing (or planning to receive during the study) ITI therapy or prophylaxis treatment with FVIII • Previous or current treatment for thromboembolic disease or signs of thromboembolic disease • Known HIV or hepatitis B or C • Use of systemic immunomodulators • Participants who are at high risk for TMA	Primary Outcome Measures • Expansion Part: Number of Bleeding Events Over Time Secondary Outcome Measures • Haemo-QoL-SF Questionnaire Score • Preference Survey Score • EQ-5D-5L Score • Number of Days Away From School/Work • Number of Days Hospitalized • Number of Participants with AEs • Number of Participants With Anti-FVIII Antibodies • Number of Participants With Anti-drug Antibodies to Emicizumab	July 4, 2018

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Efficacy, Safety, and Pharmacokinetic Study of Prophylactic Emicizumab Versus No Prophylaxis in Hemophilia A Participants (HAVEN 5) Hoffmann-La Roche NCT03315455	Phase III Randomized Multicenter Open-Label Estimated Enrollment: 70	1. Experimental: Prophylactic Emicizumab 1.5 mg/kg QW 2. Experimental: Prophylactic Emicizumab 6 mg/kg Q4W 3. Control Arm: No Prophylaxis	Inclusion Criteria • Diagnosis of severe congenital hemophilia A or hemophilia A with FVIII inhibitors • Body weight greater than or equal to >= 40 kilograms at the time of screening • Participants without FVIII inhibitors (< 0.6 Bethesda unit per milliliter [BU/mL]) who completed successful ITI must have done so at least 5 years before screening • Documentation of the details of episodic therapy (FVIII or BPAs) and of number of bleeding episodes for at least the last 24 weeks and >=5 bleeds in the last 24 weeks prior to study entry • Adequate hematologic, hepatic, and renal function Exclusion Criteria • Planned surgery during the study • Use of systemic immunomodulators with the exception of anti-retroviral therapy • Previous or current treatment for thromboembolic disease or signs of thromboembolic disease • Known HIV infection with cluster of differentiation (CD)4 count <200 cells/microliter (cells/mcL) within 24 weeks prior to screening. • Pregnant or lactating, or intending to become pregnant during the study	Primary Outcome Measures • Numbers of Treated Bleeds Over Time Secondary Outcome Measures • Reduction from Baseline in Number of All Bleeds • Reduction From Baseline in Number of Spontaneous Bleeds • Reduction from Baseline in Number of Joint Bleeds • Reduction from Baseline in Number of Target Joint Bleeds • Change from Baseline in Haemo-A-QoL Questionnaire Score in Participants (>/=) 18 Years of Age • Change from Baseline in Haemo-QoL-SF Questionnaire Score in Participants 12-17 Years of Age • Change from Baseline in EQ-5D-5L • Percentage of Participants with AEs	August 28, 2019

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
A Clinical Trial to Evaluate Prophylactic Emicizumab Versus no Prophylaxis in Hemophilia A Participants Without Inhibitors (HAVEN 3) Hoffmman-La Roche NCT02847637	Phase III Randomized Parallel Assignment Open Label Estimated Enrollment: 145	1. Emicizumab: Participants will receive emicizumab prophylaxis at the specified dose subcutaneously until the end of the study. 2. No Prophylaxis: Participants who received episodic treatment with FVIII prior to study entry will be randomized to continue episodic FVIII treatment when they start the trial; they will have the opportunity to switch to emicizumab prophylaxis after 24 weeks on-study.	Inclusion Criteria • Body weight >/= 40 kg at the time of screening • Documentation of the details of prophylactic or episodic FVIII treatment and of number of bleeding episodes for at least the last 24 weeks • Adequate hematologic, hepatic, and renal function Exclusion Criteria • Pregnant or lactating, or intending to become pregnant during the study • Use of systemic immunomodulators at enrollment or planned use during the study, with the exception of anti-retroviral therapy • Participants who are at high risk for TMA in the investigator's judgment • Concurrent disease, treatment, or abnormality in clinical laboratory tests that would prevent the participant's safe participation in and completion of the study	Primary Outcome Measures • Number of Bleeds Over Time Secondary Outcome Measures • Reduction in Number of Bleeds Over Time • Haemo-A-QoL Questionnaire Score in Participants >=18 Years of Age • Haemo-QoL-SF Questionnaire Score in Participants 12-17 Years of Age • EQ-5D-5L Score • Percentage of Participants With AEs	*September 15, 2017 *This study is ongoing, but not recruiting participants.

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

Appendix E. Comparative Clinical Effectiveness Supplemental Information

We performed screening at both the abstract and full-text level. Two investigators 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 (for example, FDA prescribing information, manufacturer's submission to the agency).

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 E1)[74] 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. Nevertheless, we restricted our use of case series to those that met specific criteria, including a minimum of six months follow-up, clearly defined entry criteria, and use of consecutive samples of patient

Table E1. Evidence Tables

Author & Year of Publication (Trial) Quality Rating	Study Design and Duration of Follow-up	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Oldenburg NEJM 2017[13] **(HAVEN 1)** ***Good quality*** **The additional comparison in HAVEN 1* (emicizumab prophylaxis vs. prior BPA) was rated as *fair quality*** ***Not shown in abstraction table** **(Additional reference)[79]**	Phase 3, open-label, multicenter, randomized trial Median follow up: 24 weeks (3 – 47.9 weeks) 43 sites in 14 countries (United States, Australia, Costa Rica, France, Germany, Italy, Japan, Korea, New Zealand, Poland, South Africa, Spain, Taiwan, United Kingdom)	1) Emicizumab SC prophylaxis (n = 35) 2) No prophylaxis (n=18) 3) Emicizumab SC prophylaxis (prior BPA prophylaxis) (n=49) 4) Emicizumab SC prophylaxis (unable to enroll to A, B & C group) (n=7) Emicizumab was given at 3mg/kg for 4 weeks, followed by 1.5mg/kg weekly. Patients could receive episodic treatment with BPAs for breakthrough bleeding, as needed	**Inclusion** -12 years of age or older -Congenital Hemophilia A (of any severity), plus a history of a high titer of factor VIII inhibitor (≥5 Bethesda/ml) -Receiving episodic or prophylactic treatment with BPAs **Exclusion** -Inherited or acquired bleeding disorder other than hemophilia A -Ongoing (or plan to receive during study) immune tolerance induction therapy or prophylaxis with factor VIII -Treatment within the last 12 months for, or current signs of, thromboembolic disease	**Median Age** (1) 38 (2) 36 (3) 17 (4) 26 **Male, %** 100% male in all groups **Target Joint, %** (1) 71 (2) 72 (3) 69 (4) 57 **Previous ITI** (1) 40 (2) 39 (3) 67 (4) 43 **Severe Hemophilia, %** 1) 89 2) 100 3) 96 4) 86 **≥9 bleeds in 24 wks prior to trial, %** (1) 69 (2) 72 (3) 53 (3) 43	**Model based ABR (95% CI)** *Treated bleeds* 1) 2.9† (1.7 - 5.0) 2) 23.3 (12.3 - 43.9) 3) 5.1 (2.3 - 11.2) *All (treated & untreated)* 1) 5.5† (3.6 - 8.6) 2) 28.3 (16.8 - 47.8) 3) 6.5 (3.4 - 12.4) *Treated spontaneous bleeds* 1) 1.3† (0.7 - 2.2) 2) 16.8 (9.9 - 28.3) 3) 3.1 (1.2 - 8.0) **†p value 1 vs. 2 <0.0001** *Treated joint bleeds* 1) 0.8* (0.26 - 2.2) 2) 6.7 (2.0 - 22.4) 3) 0.6 (0.2 - 1.5) *Treated target joint bleeds* 1) 0.1* (0.03 - 0.58) 2) 3.0 (0.96 - 9.13) 3) 0.3 (0.1 – 0.95) ***p value 1 vs. 2 = 0.002** **Diff. in quality of life (1 vs 2)** *Haem-A-QOL, (95% CI)* Physical health: 21.6 (7.9 - 35.2) Total score: 14 (5.6 – 22.4) *EQ-DD-DL, (95% CI)* VAS score: -9.7 (-17.6 - -1.8) Index utility score: -0.16 (-0.25 – 0.07) *Missed work/school days (%)* 1) 7/4	**AE population (n)** 1) 34 2) 13† 3) 49 4) 7 †after switch to emi Total N: 103 ***≥1 AE, %*** 1) 85 (2) 54 3) 71 (4) 29 ***≥ 1 SAE, %*** 1) 11.8 (2) 7.7 3) 8.2 (4) 0 ***Thrombotic microangiopathy in all patients:*** 1.9% ***Common AE in ≥5%*** -Injection-site reaction: 15% -Headache: 12% -Fatigue: 6% -URTI: 9% -Arthralgia: 6%

Author & Year of Publication (Trial) Quality Rating	Study Design and Duration of Follow-up	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
					2) 14/33 *Mean days of hospitalization (SD)* 1) 1.9 (8.9) 2) 4.2 (9.5)	
Young 2017 **HAVEN 2** **Interim analysis** **Conference abstract**	Phase 3, single arm, open-label, multicenter trial ≥52 weeks (ongoing) Median observation 9 weeks (1.6 -41.6)	Emicizumab prophylaxis (n= 60) Emicizumab was given at 3mg/kg weekly for 4 weeks, followed by 1.5mg/kg weekly.	**Inclusion** -2-12 years old (or 12–17 years if <40 kg) *currently enrolling those <2 years of age - previously treated with BPAs	**Median Age:** 7 (1 – 15) **Age groups in the interim analysis:** <12 years (n=57) >12 years (n=3) <2 years (n=2)	**Result for <12 years patients on study for ≥12 weeks (n=23)** **Model based ABR (95% CI)** *Treated bleeds* 0.2 (0.06 – 0.62) *All (treated & untreated)* 2.9 (1.75 – 4.94) *Treated spontaneous bleeds* 0.1 (0.01 - 0.47) *Treated joint bleeds* 0.1 (0.01 – 0.47) **Median ABR (IQR)** *Treated bleeds* 0.0 (0.00 – 0.00) *All (treated & untreated)* 1.5 (0.00 – 4.53) *Treated spontaneous bleeds* 0.0 (0.00 - 0.00) *Treated joint bleeds* 0.0 (0.00 – 0.00) **99% ABR reduction compared to BPA period** **Patients with zero treated bleed, n (%)** 54 (94.7)	***Most Common AE*** -Injection-site reaction: 17% -URTI: 17% ***Serious AE***: 7 patients 2 muscle hemorrhage, 1 eye pain, 1 catheter site infection, 1 device-related infection, 1 mouth hemorrhage, 1 appendicitis

Author & Year of Publication (Trial) Quality Rating	Study Design and Duration of Follow-up	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
					Patients with Zero ALL bleeds, n (%) 37 (64.9)	
Mancuso 2018[78] **HAVEN 2** **Conference abstract**	Phase 3, single arm, open-label, multicenter trial ≥52 weeks (ongoing) Median observation 9 weeks (1.6 -41.6)	Emicizumab prophylaxis (n= 60) Emicizumab was given at 3mg/kg weekly for 4 weeks, followed by 1.5mg/kg weekly.	*See Young 2017*	*See Young 2017*	**Haem-A-QOL, (95% CI)* Physical health: -19.6 (-42.9;3.6) Total score: -9.8 (-20.2; 0.4) **Adapted Inhib-QoL (95%CI)* Physical health: -31.7 (-43.4; -20) Dealing with Inhibitor: -26.8 (-34.9; -18.8) Family life: -25.8 (-38.3; -13.3) Total score: -21.8 (-28.3; -15.4) Patients with no missed school days, (%) Baseline: 27.5 Week 25: 83.3 *Values reported as mean change from baseline to week 25	*See Young 2017*

Author & Year of Publication (Trial) Quality Rating	Study Design and Duration of Follow-up	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
Antunes Haemophilia 2014[18] **PROOF** ***Fair quality***	Phase 3, open-label, multicenter, randomized trial 12 months 17 sites in 10 countries (United States, Brazil, Bulgaria, Croatia, Japan, New Zealand, Poland, Romania, Russian, Ukraine)	1) aPCC Prophylaxis (n=17) 2) No prophylaxis (On-demand) (n=19) Prophylaxis dosing was 85 +/-15 U/kg by IV bolus infusion every other day. Patients on prophylaxis could receive episodic treatment for bleeding events. On-demand dosing as well as dosing for the treatment of bleeding while on prophylaxis was dependent upon the type of bleeding and was at the discretion of the investigator	**Inclusion** - ≥4 and ≤65 years -Hemophilia A or B with >5 BU inhibitor. -If low-titer inhibitor (≤5 BU), refractory to increased dosing of either FVIII or FIX for at least 12 months - Currently on on-demand treatment with BPAs - ≥12 bleeding episodes in the previous 12 months **Exclusion** -Symptomatic liver disease -Platelet count <100 000 mL/ml -Currently receiving ITI or prophylaxis -Previous thromboembolic events	**Median Age** 1) 23.5 2) 23.5 **Male, %** 100% male in all groups **Target Joint, %** 1) 76.5 2) 73.7 **Severe Hemophilia, %** 1) 94.1 2) 89.5 **Hemophilia A, %** 1) 94.1 2) 89.5	**Median ABR (IQR)** *All* 1) 7.9 (32.3) 2) 28.7 (8.1) **p value=0.003** *Spontaneous* 1) 5.6 (5.1) 2) 18.9 (32.6) **p value=0.008** *Traumatic* 1) 2.5† (3.1) 2) 4.7 (8.7) *Joint bleed* 1) 6 (7.1) 2) 22.9 (32.8) *Non-joint bleed* 1) 0.5 (2) 2) 2.9 (4) *New target joint* 1) 0 2) 5.9 **p value<0.03** **New target joint, %** 1) 29.4% 2) 57.9%	***≥1 AE, %*** 63.9 ***≥1 SAE, %*** 47.2 ***Common non-serious AE, %*** Headache: 2.8 Dizziness: 2.8 Hypersensitivity: 2.8 Hypotension: 2.8 Rash: 2.8 ***Serious AE, %*** HBsAB positive: 13.9 Hemarthrosis: 8.3 Other SAE occurring in 2.8% of the population each include: abdominal wall hematoma, cholecystitis, hematoma infection, femoral neck fracture, hemarthrosis, hematuria, hematoma, hemorrhage, hypertensive crisis
Stasyshyn Haemophilia 2014[82] **PROOF**	Phase 3, open-label, multicenter, randomized trial 12 months	1) aPCC Prophylaxis (n=17) 2) No prophylaxis (On-demand) (n=19)	*See Antunes Haemophilia 2014*	*See Antunes Haemophilia 2014*	At 12 months **Mean EQ-5D change** 1) 0.08 (±0.26) 2) -0.01 (±0.25) Both NS, but greater than MID (0.07)	*See Antunes Haemophilia 2014*

Author & Year of Publication (Trial) Quality Rating	Study Design and Duration of Follow-up	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
See Antunes Haemophilia 2014	17 sites in 10 countries (United States, Brazil, Bulgaria, Croatia, Japan, New Zealand, Poland, Romania, Russian, Ukraine)	Prophylaxis dosing was 85 +/-15 U/kg by IV bolus infusion every other day. Patients on prophylaxis could receive episodic treatment for bleeding events. On-demand dosing as well as dosing for the treatment of bleeding while on prophylaxis was dependent upon the type of bleeding and was at the discretion of the investigator			**Mean EQ-VAS change** 1) 15.7 (±18.7), p=0.013 2) 5.8 (±21.3), NS MID: 7.0 **Pain VAS** 1) 23.2 (±46.6), p=0.021 2) NS **Haem-A-QoL measures** Total score 1) 9.5 (±12.8), p<0.05 2) NS Physical Health Score 1) 21.9 (±24.8), p<0.05 2) NS	
Leissinger NEJM 2011[11] **Pro-FEIBA** ***Fair quality***	Open label, Randomized, Cross-over Study Duration of follow-up: 3 months 16 hemophilia treatment centers in Europe and the United States	***1st study period*** 1) Prophylaxis (n=17) (months 1-6) 2) On-demand therapy (n=17) (months 1-6) Washout (months 7-9) ***2nd study period*** 1) On-demand therapy (n=14) (months 10-15) 2) Prophylaxis (n=14) (months 10-15)	**Inclusion Criteria** - Diagnosis of severe hemophilia A -History of a factor VIII inhibitor titer exceeding 5 BU ->2 years of age -Being treated with bypassing therapy, -Six or more episodes of bleeding requiring bypassing treatment in the 6-month period before study enrollment **Exclusion Criteria**	**Median age, (range)** 28.7 (2.8-67.9) **Median time from development of factor VIII inhibitors to study enrollment (range)** 11.2 years (0.2-31.7)	**Mean number of bleeding events (±SD)** 1) 5.0±5.0 2)13.1±7.1 (p-value: P<0.001) **Mean number of hemarthroses (±SD)** 1) 4.2±4.3 2) 10.8±7.6 (p-value: P<0.001) **Mean rates of joint hemorrhages per month (±SD)** 1) 0.7±0.7 2) 1.6±1.3	**AEs, n (%)** 21 (62) **Pyrexia, n (%)** 6 (18) **Cough, n (%)** 5 (15) **Influenza, n (%)** 5 (15) **Serious AEs, n (%)** 9 (26) **Catheter-site infection, n (%)**

Author & Year of Publication (Trial) Quality Rating	Study Design and Duration of Follow-up	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
		6 months AICC prophylaxis at a target of 85 U per kilogram of body weight (±15%) on 3 nonconsecutive days per week, compared with 6 months of on-demand therapy with AICC, separated by a 3-month washout period. *26 patients completed both periods	-Receiving immune tolerance therapy -Receiving regular prophylaxis with any hemostatic agent -Diagnosis of symptomatic liver disease -Platelet count <100,000 per cubic millimeter -Planned to undergo elective surgery within 12 months, -Planned to begin treatment with interferon or a protease inhibitor		(p-value: P<0.001)	3 (9) **Muscle hemorrhage, n (%)** 2 (6) **Catheter-site hemorrhage, n (%)** 2 (6)
Gringeri Haemophilia 2013 [80] **Pro-FEIBA** ***See Leissinger NEJM 2011***	Open label, Randomized, Cross-over Study Duration of follow-up: 3 months 16 hemophilia treatment centers in Europe and the United States	1) Prophylaxis (n=17) (months 1-6) 2) On-demand therapy (n=17) (months 1-6) Washout (months 7-9) 1) On-demand therapy (n=14) (months 10-15) 2) Prophylaxis (n=14) (months 10-15) Dosing: 6 months AICC prophylaxis at a target dose of 85 U kg^{-1} (±15%) on 3	*See Leissinger NEJM 2011*	*See Leissinger NEJM 2011*	**Mean SF-36 change between post and pre (SD)** ***On-demand*** PCS: 1.5 (9.1), p value=0.356 MCS:1.5 (8.0), p value=0.906 ***Prophylaxis*** PCS: 4.4 (8.4), p value=0.356 MCS: 2.7 (7.6), p value=0.906 **Mean EQ-5D change between post and pre (SD)** ***On-demand*** VAS: 10.6 (17.4) Utility: 0.01 (0.26) ***Prophylaxis*** VAS: 9.0 (18.2) Utility: 0.01 (0.12)	*See Leissinger NEJM 2011*

<table>
<tr><th>Author & Year of Publication (Trial) Quality Rating</th><th>Study Design and Duration of Follow-up</th><th>Interventions (n) & Dosing Schedule</th><th>Inclusion and Exclusion Criteria</th><th>Patient Characteristics</th><th>Outcomes</th><th>Harms</th></tr>
<tr><td></td><td></td><td>nonconsecutive days per week, compared with 6 months of on-demand therapy with AICC, separated by a 3-month washout period.</td><td></td><td></td><td>Mean number of missed days due to condition/tx, (SD)
1) 4.2 (6.6)
2) 19.3 (19.4)
(p value= 0.010)</td><td></td></tr>
<tr><td>Konkle J Thromb Haemost 2007 [75]

Fair quality</td><td>Multicenter, randomized, double-blind, parallel-group trial

20 sites in 11 countries: (Argentina, Brazil, Bulgaria, the Philippines, Poland, Romania, Russia, South Africa, Spain, Turkey, USA).</td><td>1) Pre-prophylaxis period (n=37)

*2) 3-month Prophylaxis period: a) 90 mcg kg rFVIIa (n=11); b) 270 mcg kg rFVIIa (n=11)

3) 3-month post-prophylaxis period (n=22)

*Patients received 90 or 270 mcg kg rFVIIa once daily for 3 months. Each rFVIIa dose was to be self-administered before 11 AM in a home setting as a slow bolus IV injection over a period of 2 min.

<u>Note:</u> Concomitant administration of other</td><td>Inclusion Criteria
-Males with severe congenital hemophilia A or B with a high historical inhibitor titer
- Requirement for current treatment of bleeds with BPAs
- At least four bleeds requiring hemostatic drug treatment within the previous month

Exclusion Criteria
- Prophylaxis with any hemostatic drug within the last 3 months
-ITI within the last month
-Known pseudotumors
-Advanced atherosclerotic disease
-Congenital or acquired coagulation disorders other than hemophilia A or B</td><td>Median age, yrs (range)
15.7 (5.1-56.1)

Median body weight, kg (range)
54.0 (17.4-79.2)

Hemophilia type, no. (%)
A: 21 (95)
B: 1 (5)

Target joint, no. (%)
Yes: 21 (95)
No: 1 (5)

*Data reported above reflects total number of patients (n=22) in the 3-month prophylaxis period receiving both doses.</td><td>Change in bleeds per month
Patients on 90 mcg/kg rFVIIa
1) 5.6
2) 3.0
Patients on 270 mcg kg rFVIIa
1) 5.3
2) 2.2

*Number of Bleeds by period
<table><tr><th></th><th>Total</th><th>TJ</th><th>SP</th></tr><tr><td>Pre</td><td>408</td><td>208</td><td>276</td></tr><tr><td>Pro</td><td>181</td><td>106</td><td>124</td></tr><tr><td>Post</td><td>232</td><td>126</td><td>158</td></tr></table>TJ=Target joint; SP=Spontaneous
*Table represents total number of bleeds for both doses.

Mean proportion of absentee days, %
1) 38.7
2) 16.7
(p value= 0.0127)

Mean proportion of days in hospital, %</td><td>*Pre-prophylaxis period
AEs, n
8; 9
Thrombotic/Thromboembolic
0; 0
SAEs
0; 0

Prophylaxis period
AEs, n
2.a) 9 2.b) 8
Thrombotic/Thromboembolic
2.a) 0 2.b) 0
SAEs
2.a) 0 2.b) 4

*Post-Prophylaxis period
AEs, n
7; 3
Thrombotic/Thromboembolic
0; 0
SAEs
0; 1

*Data reported for patients who completed all phases of study (pre, pro, post) and had been randomized to the 2</td></tr>
</table>

Author & Year of Publication (Trial) Quality Rating	Study Design and Duration of Follow-up	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
		hemostatic drugs was permitted during the entire trial period, except from 1 h prior to and until 2 h after rFVIIa administration.			1) 13.5 2) 5.9 (p value= 0.0026)	dosage groups (90 vs. 270 mcg kg rFVIIa).
Hoots Haemophilia 2008 [81] ***See Konkle J Thromb Haemost 2007***	Multicenter, randomized, double-blind, parallel-group trial 20 sites in 11 countries: (Argentina, Brazil, Bulgaria, the Philippines, Poland, Romania, Russia, South Africa, Spain, Turkey, USA).	1) Pre-prophylaxis period (n=37) *2) 3-month Prophylaxis period: a) 90 mcg kg rFVIIa (n=11); b) 270 mcg kg rFVIIa (n=11) 3) 3-month post-prophylaxis period (n=22) *Patients received 90 or 270 mcg kg rFVIIa once daily for 3 months. Each rFVIIa dose was to be self-administered before 11 AM in a home setting as a slow bolus IV injection over a period of 2 min. Note: Concomitant administration of other	*See Konkle J Thromb Haemost 2007*	*See Konkle J Thromb Haemost 2007*	**Median number of days of bleeding-related hospitalization** 1) 9.5 days 2) 1.5 days **Proportion of days absent from school or work, %** 1) 38.7 2) 16.7 **Median number of absentee days from school or work** 1) 18.5 2) 4.5 **Mean change in EQ-5D Score VAS** 1) 64.59 2) 67.95 (p-value=0.257) 3) 71.59 (p-value=0.048) **TTO** 1) 0.56 2) 0.61 (p-value=0.456) 3) 0.69 (p-value=0.054)	*See Konkle J Thromb Haemost 2007*

Author & Year of Publication (Trial) Quality Rating	Study Design and Duration of Follow-up	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms
		hemostatic drugs was permitted during the entire trial period, except from 1 h prior to and until 2 h after rFVIIa administration.				

Appendix F. Comparative Value Supplemental Information

Table F1. Impact Inventory (adapted from Neumann, Sanders et al.[102])

Sector	Type of Impact	Included in This Analysis from… Perspective?	
		Health Care Sector	Societal
Formal Health Care Sector			
Health Outcomes	Longevity effects	☑	☐
	Health-related quality of life effects	☑	☑
	Adverse events	☐	☐
Medical Costs	Paid by third-party payers	☑	☐
	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 Sectors			
Productivity	Labor market earnings lost	NA	☐
	Cost of unpaid lost productivity due to illness	NA	☑
	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

Table F2. Detailed Base Case Results Per Regimen in Target Population ≥ 12 Years Old

	Emicizumab Prophylaxis		BPA Prophylaxis		No Prophylaxis	
	Deterministic	95% Credible Range	Deterministic	95% Credible Range	Deterministic	95% Credible Range
Total Cost	**$19,221,932**	**($15,144,711 - $22,974,418)**	**$90,182,398**	**($67,881,842 - $110,735,948)**	**$28,135,154**	**($15,507,413 - $37,485,495)**
Prophylaxis Cost	$14,952,461	($12,032,088 - $18,387,563)	$81,418,150	($61,034,215 - $99,839,799)	--	--
Treated Bleed Not into Target Joint Cost	$3,623,370	($1,670,709 - $5,569,385)	$6,848,585	($1,712,250 - $12,220,168)	$21,754,441	($9,503,400 - $31,389,649)
Treated Target Joint Bleed Cost	$193,760	($49,060 - $492,345)	$1,058,821	($219,975 - $2,822,669)	$3,771,321	($1,001,738 - $9,346,787)
Non-Pharmacy Cost	$374,914	($181,211 - $570,535)	$776,655	($318,530 - $1,289,261)	$2,507,107	($1,329,982 - $3,442,093)
Orthopedic Surgery Cost	$77,427	($61,804 - $97,131)	$80,187	($63,168 - $102,615)	$102,286	($79,558 - $130,155)
Adverse Event Cost	$844	($167 - $2,099)	$0	$0	$0	$0
Total QALYs	**15.41**	**(14.33 - 16.53)**	**15.21**	**(14.14 - 16.32)**	**14.50**	**(13.22 - 15.87)**
No Bleed/Untreated Bleed Health States	14.70	(13.66 - 15.91)	13.71	(12.27 - 15.28)	9.57	(7.65 - 12.26)
Treated Bleed Not into Target Joint Health State	0.73	(0.32 - 1.11)	1.38	(0.34 - 2.42)	4.34	(1.84 - 6.22)
Target Joint Bleed Health State	0.03	(0.01 - 0.09)	0.19	(0.04 - 0.49)	0.66	(0.17 - 1.60)
Orthopedic Surgery	-0.055	(-0.069 - -0.043)	-0.057	(-0.072 - -0.045)	-0.073	(-0.095 - -0.056)
Total Life Years	**21.28**	**(20.04 - 22.53)**	**21.28**	**(20.04 - 22.53)**	**21.28**	**(20.04 - 22.53)**
Maximum Pettersson Score	**42**	**(38 - 49)**	**46**	**(38 - 58)**	**75**	**(57 - 78)**
Total Bleed Events	**107**	**(52 - 158)**	**221**	**(88 - 360)**	**713**	**(405 - 936)**
Treated Bleeds Not into Target Joint	101	(46 - 153)	191	(47 - 337)	608	(261 - 855)
Treated Target Joint Bleeds	5	(1 - 14)	30	(6 - 81)	105	(29 - 258)

BPA: bypassing agent, QALY: quality-adjusted life year

Table F3. Detailed Base Case Results Per Regimen in Target Population < 12 Years Old

	Emicizumab Prophylaxis		BPA Prophylaxis		No Prophylaxis	
	Deterministic	95% Credible Range	Deterministic	95% Credible Range	Deterministic	95% Credible Range
Total Cost	**$20,683,787**	**($16,282,274 - $24,689,826)**	**$99,212,053**	**($76,026,579 - $121,419,561)**	**$30,684,758**	**($16,128,080 - $40,979,605)**
Prophylaxis Cost	$16,461,362	($13,227,751 - $20,185,207)	$89,865,693	($68,717,090 - $111,203,456)	--	--
Treated Bleed Not into Target Joint Cost	$3,737,321	($1,686,808 - $5,778,969)	$7,562,624	($1,658,406 - $13,988,201)	$24,022,576	($10,257,063 - $34,333,928)
Treated Target Joint Bleed Cost	$197,053	($49,498 - $485,357)	$1,169,214	($252,101 - $3,180,176)	$4,164,521	($1,097,103 - $9,986,080)
Non-Pharmacy Cost	$288,051	($140,279 - $432,371)	$614,521	($239,186 - $1,071,304)	$2,448,224	($1,078,276 - $2,711,746)
Orthopedic Surgery Cost	$0	($ - $39)	$0	($ - $839)	$49,437	($15,772 - $89,040)
Adverse Event Cost	$844	($163 - $2,028)	$0	$0	$0	$0
Total QALYs	**22.79**	**(19.93 - 24.95)**	**22.41**	**(20.39 - 24.17)**	**20.40**	**(19.19 - 21.76)**
No Bleed/Untreated Bleed Health States	21.82	(19.07 - 24.15)	20.11	(17.57 - 22.75)	13.40	(10.74 - 17.24)
Treated Bleed Not into Target Joint Health State	0.93	(0.42 - 1.43)	2.02	(0.46 - 3.71)	6.07	(2.62 - 8.38)
Target Joint Bleed Health State	0.04	(0.01 - 0.10)	0.28	(0.06 - 0.73)	0.93	(0.24 - 2.23)
Orthopedic Surgery	0.000	(0.000 - 0.000)	0.000	(-0.001 - 0.000)	-0.001	(-0.002 - -0.001)
Total Life Years	**28.06**	**(27.40 - 28.73)**	**28.06**	**(27.40 - 28.73)**	**28.06**	**(27.40 - 28.73)**
Maximum Pettersson Score	**16**	**(8 - 28)**	**23**	**(9 - 44)**	**74**	**(42 - 78)**
Total Bleed Events	**177**	**(88 - 265)**	**392**	**(152 - 677)**	**1267**	**(696 - 1678)**
Treated Bleeds Not into Target Joint	168	(77 - 255)	340	(75 - 624)	1080	(470 - 1509)
Treated Target Joint Bleeds	9	(2 - 22)	53	(11 - 139)	187	(50 - 445)

BPA: bypassing agent, QALY: quality-adjusted life year

Table F4. Detailed Base Case Incremental Results in Target Population ≥ 12 Years Old

	Emicizumab vs. No Prophylaxis		Emicizumab vs. BPA Prophylaxis	
	Deterministic	95% Credible Range	Deterministic	95% Credible Range
Incremental C-E Ratio	**-$9,800,611**	**(-$51,665,927 - $4,753,357)**	**-$363,487,901**	**(-$5,032,270,941 - $841,216,075)**
Incremental Cost	**-$8,913,222**	**(-$17,209,843 - $2,502,217)**	**-$70,960,466**	**(-$91,327,369 - -$49,928,425)**
Prophylaxis Cost	$14,952,461	($12,032,088 - $18,387,563)	-$66,465,690	(-$84,591,937 - -$46,723,703)
Treated Bleed Cost (non-Target Joint)	-$18,131,070	(-$25,878,962 - -$7,573,511)	-$3,225,215	(-$7,491,929 - $694,437)
Treated Target Joint Bleed Cost	-$3,577,560	(-$8,833,586 - -$959,904)	-$865,060	(-$2,395,438 - -$154,539)
Non-Pharmacy Cost	-$2,132,194	(-$2,910,465 - -$1,145,824)	-$401,742	(-$844,258 - -$28,916)
Orthopedic Surgery Cost	-$24,858	(-$37,918 - -$14,093)	-$2,760	(-$9,378 - $3,141)
Adverse Event Cost	$844	($167 - $2,099)	$844	($167 - $2,099)
Incremental QALYs	**0.91**	**(0.09 - 1.72)**	**0.20**	**(-0.01 - 0.51)**
No Bleed/Untreated Bleed Health States	5.12	(3.00 - 6.63)	0.99	(0.11 - 1.95)
Treated Bleed Not into Target Joint Health State	-3.61	(-5.20 - -1.48)	-0.65	(-1.49 - 0.14)
Target Joint Bleed Health State	-0.63	(-1.52 - -0.16)	-0.15	(-0.42 - -0.03)
Orthopedic Surgery	0.018	(0.010 - 0.027)	0.002	(-0.002 - 0.007)
Incremental Life Years	**0.00**	**(0.00 - 0.00)**	**0.00**	**(0.00 - 0.00)**
Incremental Bleed Events	**-606**	**(-796 - -345)**	**-114**	**(-233 - -11)**
Treated Bleeds Not into Target Joint	-507	(-721 - -207)	-90	(-206 - 20)
Treated Target Joint Bleeds	-100	(-244 - -27)	-24	(-70 - -5)

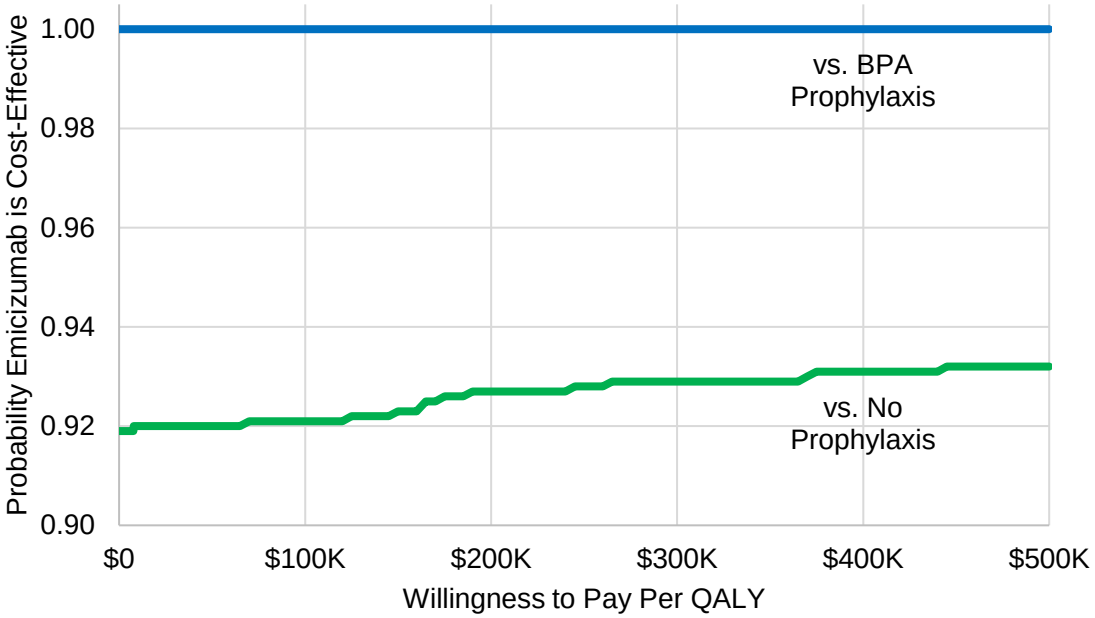
BPA: bypassing agent, C-E: cost-effectiveness, QALYs: quality-adjusted life years

Table F5. Detailed Base Case Incremental Results in Target Population < 12 Years Old

	Emicizumab vs. No Prophylaxis		Emicizumab vs. BPA Prophylaxis	
	Deterministic	95% Credible Range	Deterministic	95% Credible Range
Incremental C-E Ratio	**-$4,190,565**	**(-$24,874,574 - $11,778,398)**	**-$210,559,527**	**(-$3,007,764,626 - $2,204,335,552)**
Incremental Cost	**-$10,000,971**	**(-$18,861,008 - $3,204,083)**	**-$78,528,265**	**(-$100,616,891 - -$55,887,087)**
Prophylaxis Cost	$16,461,362	($13,227,751 - $20,185,207)	-$73,404,331	(-$95,027,202 - -$52,147,310)
Treated Bleed Cost (non-Target Joint)	-$20,285,256	(-$28,739,494 - -$8,440,310)	-$3,825,303	(-$9,377,086 - $988,692)
Treated Target Joint Bleed Cost	-$3,967,468	(-$9,505,710 - -$1,045,043)	-$972,161	(-$2,796,418 - -$186,215)
Non-Pharmacy Cost	-$2,160,173	(-$2,289,248 - -$924,915)	-$326,470	(-$709,550 - -$9,741)
Orthopedic Surgery Cost	-$49,437	(-$89,040 - -$15,772)	$0	(-$834 - $0)
Adverse Event Cost	$844	($163 - $2,028)	$844	($163 - $2,028)
Incremental QALYs	**2.39**	**(-0.67 - 4.43)**	**0.37**	**(-0.53 - 1.48)**
No Bleed/Untreated Bleed Health States	8.41	(4.16 - 11.06)	1.70	(0.03 - 3.68)
Treated Bleed Not into Target Joint Health State	-5.14	(-7.03 - -2.18)	-1.09	(-2.54 - 0.22)
Target Joint Bleed Health State	-0.89	(-2.13 - -0.23)	-0.24	(-0.64 - -0.05)
Orthopedic Surgery	0.001	(0.001 - 0.002)	0.000	(0.000 - 0.001)
Incremental Life Years	**0.00**	**(0.00 - 0.00)**	**0.00**	**(0.00 - 0.00)**
Incremental Bleed Events	**-1090**	**(-1427 - -604)**	**-215**	**(-449 - -15)**
Treated Bleeds Not into Target Joint	-911	(-1250 - -394)	-172	(-407- 49)
Treated Target Joint Bleeds	-178	(-248 - -29)	-44	(-71 - -5)

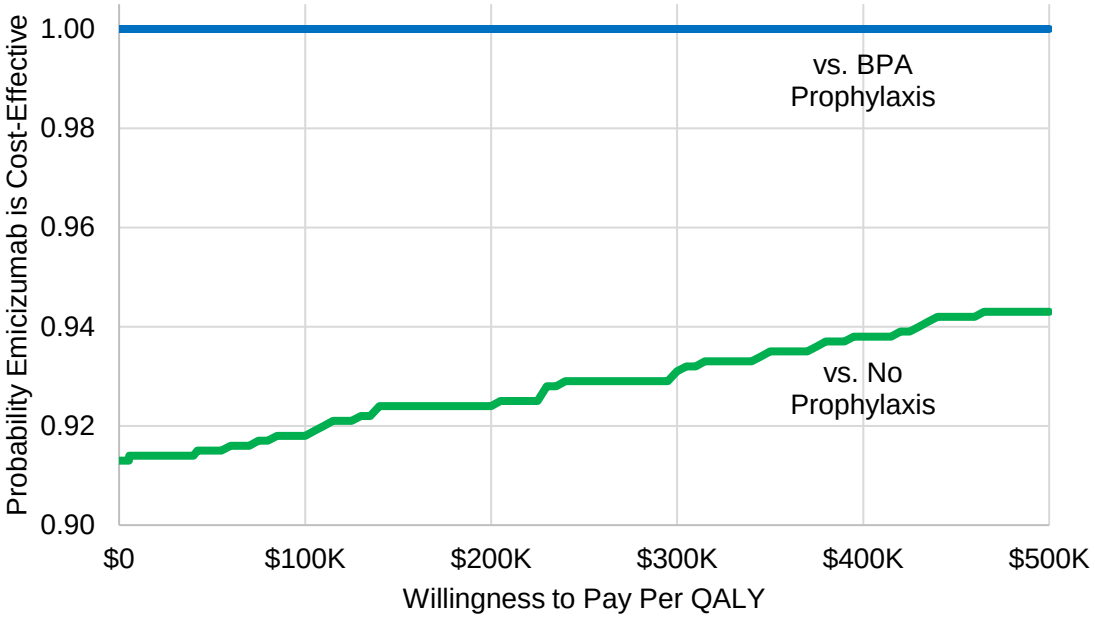
BPA: bypassing agent, C-E: cost-effectiveness, QALYs: quality-adjusted life years

Figure F1. Probabilistic Sensitivity Analysis Results in Target Population ≥ 12 Years Old



BPA: bypassing agent, QALY: quality-adjusted life year

Figure F2. Probabilistic Sensitivity Analysis Results in Target Population < 12 Years Old



BPA: bypassing agent, QALY: quality-adjusted life year

Table F6. Detailed Societal Perspective Results Per Regimen in Target Population ≥12 Years Old

	Emicizumab Prophylaxis		BPA Prophylaxis		No Prophylaxis	
	Deterministic	95% Credible Range	Deterministic	95% Credible Range	Deterministic	95% Credible Range
Total Cost	**$19,623,275**	**($15,898,743 - $23,118,938)**	**$90,583,742**	**($69,669,227 - $110,391,941)**	**$28,901,756**	**($16,312,606 - $38,089,975)**
Prophylaxis Cost	$14,952,822	($12,252,731 - $18,419,248)	$81,418,511	($62,758,020 - $100,709,940)	--	--
Treated Bleed Not into Target Joint Cost	$3,623,370	($1,576,806 - $5,505,665)	$6,848,585	($1,404,912 - $11,934,766)	$21,754,441	($8,509,299 - $30,161,694)
Treated Target Joint Bleed Cost	$193,760	($47,988 - $559,633)	$1,058,821	($237,740 - $2,879,226)	$3,771,321	($978,578 - $9,896,507)
Non-Pharmacy Cost	$374,914	($179,228 - $554,114)	$776,655	($295,780 - $1,264,188)	$2,507,107	($1,360,643 - $3,479,770)
Orthopedic Surgery Cost	$77,427	($61,810 - $95,915)	$80,187	($62,760 - $101,143)	$102,286	($78,098 - $130,972)
Adverse Event Cost	$844	($172 - $2,238)	$0	$0	$0	$0
Societal Cost	**$400,983**	**($244,900 - $613,609)**	**$400,983**	**($244,900 - $613,609)**	**$766,602**	**($486,702 - $1,136,779)**
Total QALYs	**15.41**	**(14.33 - 16.57)**	**15.21**	**(14.12 - 16.42)**	**14.50**	**(13.31 - 15.79)**
No Bleed/Untreated Bleed Health States	14.70	(13.66 - 16.04)	13.71	(12.42 - 15.48)	9.57	(7.75 - 12.38)
Treated Bleed Not into Target Joint Health State	0.73	(0.33 - 1.09)	1.38	(0.29 - 2.37)	4.34	(1.77 - 5.96)
Target Joint Bleed Health State	0.03	(0.01 - 0.10)	0.19	(0.04 - 0.54)	0.66	(0.17 - 1.74)
Orthopedic Surgery	-0.055	(-0.067 - -0.043)	-0.057	(-0.070 - -0.044)	-0.073	(-0.091 - -0.055)
Total Life Years	**21.28**	**(20.03 - 22.58)**	**21.28**	**(20.03 - 22.58)**	**21.28**	**(20.03 - 22.58)**
Maximum Pettersson Score	**42**	**(38 - 49)**	**46**	**(38 - 57)**	**75**	**(57 - 78)**
Total Bleed Events	**107**	**(53 - 157)**	**221**	**(85 - 352)**	**713**	**(397 - 950)**
Treated Bleeds Not into Target Joint	101	(46 - 152)	191	(40 - 323)	608	(252 - 826)
Treated Target Joint Bleeds	5	(1 - 16)	30	(7 - 83)	105	(27 - 279)

BPA: bypassing agent, QALYs: quality-adjusted life years

Table F7. Detailed Societal Perspective Results Per Regimen in Target Population <12 Years Old

	Emicizumab Prophylaxis		BPA Prophylaxis		No Prophylaxis	
	Deterministic	95% Credible Range	Deterministic	95% Credible Range	Deterministic	95% Credible Range
Total Cost	**$21,212,892**	**($17,062,582 - $25,069,098)**	**$99,741,157**	**($75,978,520 - $120,460,774)**	**$31,231,116**	**($16,528,993 - $41,914,896)**
Prophylaxis Cost	$16,461,724	($13,334,195 - $20,115,904)	$89,866,055	($68,710,774 - $109,588,806)	--	--
Treated Bleed Not into Target Joint Cost	$3,737,321	($1,564,790 - $5,628,279)	$7,562,624	($1,591,865 - $14,493,350)	$24,022,576	($9,919,200 - $33,850,047)
Treated Target Joint Bleed Cost	$197,053	($53,907 - $508,674)	$1,169,214	($279,786 - $3,068,661)	$4,164,521	($1,187,666 - $10,146,664)
Non-Pharmacy Cost	$288,051	($130,374 - $428,431)	$614,521	($209,211 - $1,071,211)	$1,983,726	($1,017,107 - $2,681,724)
Orthopedic Surgery Cost	$0	($ - $137)	$0	($ - $786)	$49,437	($16,676 - $91,514)
Adverse Event Cost	$844	($162 - $1,974)	$0	$0	$0	$0
Societal Cost	**$528,743**	**($329,828 - $807,181)**	**$528,743**	**($329,828 - $807,181)**	**$1,010,856**	**($640,888 - $1,461,774)**
Total QALYs	**22.79**	**(19.99 - 24.83)**	**22.41**	**(20.42 - 24.19)**	**20.40**	**(19.11 - 21.74)**
No Bleed/Untreated Bleed Health States	21.82	(19.12 - 24.13)	20.11	(17.50 - 22.87)	13.40	(10.59 - 17.54)
Treated Bleed Not into Target Joint Health State	0.93	(0.40 - 1.36)	2.02	(0.43 - 3.89)	6.07	(2.42 - 8.37)
Target Joint Bleed Health State	0.04	(0.01 - 0.11)	0.28	(0.07 - 0.70)	0.93	(0.27 - 2.32)
Orthopedic Surgery	0.000	(0.000 - 0.000)	0.000	(-0.001 - 0.000)	-0.001	(-0.002 - -0.001)
Total Life Years	**28.06**	**(27.38 - 28.74)**	**28.06**	**(27.38 - 28.74)**	**28.06**	**(27.38 - 28.74)**
Maximum Pettersson Score	**16**	**(8 - 30)**	**23**	**(10 - 43)**	**74**	**(42 - 78)**
Total Bleed Events	**177**	**(82 - 255)**	**392**	**(140 - 666)**	**1267**	**(662 - 1705)**
Treated Bleeds Not into Target Joint	168	(71 - 247)	340	(74 - 635)	1080	(448 - 1515)
Treated Target Joint Bleeds	9	(2 - 24)	53	(13 - 139)	187	(54 - 459)

BPA: bypassing agent, QALYs: quality-adjusted life years

BPA-Favoring Scenario

In this scenario analysis we assumed the reduction in treated bleeds with emicizumab was only as great as the reduction seen in HAVEN 1 for all bleeds; all BPA prophylaxis has the cost of prophylaxis with aPCC only; all bleeds on emicizumab are treated with rFVIIa and all bleeds on aPCC prophylaxis are treated with aPCC; emicizumab adherence is 100% and aPCC adherence is 88% (applied to cost only); the disutility applied to bleed events is limited to 2 days and the "No Bleed" utility is applied for the remaining 5 days of each model cycle; and the rate of thrombotic and microangiopathic events is as reported in HAVEN 1.

There was little notable change from the base case results, with emicizumab remaining less costly and more effective compared to both BPA prophylaxis and no prophylaxis.

Table F8. Results for the BPA-favoring Scenario for Emicizumab Prophylaxis Compared to BPA Prophylaxis and No Prophylaxis

Treatment	Prophylaxis Drug Cost	Cost of On-Demand Treated Bleeds	Total Cost	Total Bleed Events (All)	Life Years	QALYs
Patients ≥12 years of age						
Emicizumab Prophylaxis	$14,952,461	$7,762,255	$23,364,223	163	21.28	15.44
BPA Prophylaxis	$51,074,116	$4,537,215	$56,468,173	221	21.28	15.35
No Prophylaxis	$0	$25,525,761	$28,135,154	713	21.28	14.95
Patients <12 years of age						
Emicizumab Prophylaxis	$16,461,362	$8,247,080	$25,248,460	278	28.06	22.82
BPA Prophylaxis	$56,373,313	$5,010,268	$61,998,103	392	28.06	22.62
No Prophylaxis	$0	$28,187,098	$30,684,758	1267	28.06	21.03

BPA: bypassing agent, C-E: cost-effectiveness, QALYs: quality-adjusted life years

Table F9. Incremental Cost-Effectiveness Ratios for the BPA-favoring Scenario

Treatment	Incremental Cost	Incremental Bleeds Avoided	Incremental QALYs Gained	Incremental Life Years Gained
Patients ≥12 years of age				
Emicizumab vs. BPA proph.	-$33,103,950	-58	0.09	0
Emicizumab vs. no proph.	-$4,770,931	-550	0.49	0
Incremental C-E Ratios	--	Less Costly, More Effective	Less Costly, More Effective	Less Costly, Equally Effective
Patients <12 years of age				
Emicizumab vs. BPA proph.	-$36,749,643	-114	0.20	0
Emicizumab vs. no proph.	-$5,436,299	-988	1.78	0
Incremental C-E Ratios	--	Less Costly, More Effective	Less Costly, More Effective	Less Costly, Equally Effective

BPA: bypassing agent, C-E: cost-effectiveness, QALYs: quality-adjusted life years

Supplemental Methods Information

Table F10. Weekly Drug Cost and Mortality by Age and Weight

Patient Characteristics		Weekly Prophylaxis Cost		BPA-Treated Bleed Cost	Mortality		
Age in Model	Patient Weight[28]	Emicizumab [13,30]	Bypassing Agents[11,18, 75,81]	All Comparators [83,84,103]	Annual[91]	Conversion to Weekly Pr.	Mortality RR Applied[7]
0.5	9 kg	$1,339	$8,296	$5,733	0.0065	0.00013	0.00020
5	21 kg	$3,125	$19,356	$14,300	0.0002	0.00000	0.00001
10	40 kg	$5,952	$36,869	$27,183	0.0001	0.00000	0.00000
15	71 kg	$10,565	$65,442	$48,093	0.0004	0.00001	0.00001
20	85 kg	$12,648	$78,347	$57,131	0.0010	0.00002	0.00003
25	85 kg	$12,648	$78,347	$57,131	0.0013	0.00003	0.00004
30	90 kg	$13,392	$82,955	$60,841	0.0015	0.00003	0.00005
35	90 kg	$13,392	$82,955	$60,841	0.0016	0.00003	0.00005
40	92 kg	$13,690	$84,799	$61,718	0.0021	0.00004	0.00007
45	92 kg	$13,690	$84,799	$61,718	0.0031	0.00006	0.00010
50	91 kg	$13,541	$83,877	$61,044	0.0051	0.00010	0.00016
55	91 kg	$13,541	$83,877	$61,044	0.0078	0.00015	0.00025
60	91 kg	$13,541	$83,877	$61,111	0.0113	0.00022	0.00035
65	91 kg	$13,541	$83,877	$61,111	0.0156	0.00030	0.00049
70	86 kg	$12,797	$79,268	$57,873	0.0228	0.00044	0.00072
75	86 kg	$12,797	$79,268	$57,873	0.0355	0.00069	0.00113
80	79 kg	$11,755	$72,816	$53,422	0.0583	0.00115	0.00188
85	79 kg	$11,755	$72,816	$53,422	0.0990	0.00200	0.00326
90	79 kg	$11,755	$72,816	$53,422	0.1650	0.00345	0.00564
95	79 kg	$11,755	$72,816	$53,422	0.2554	0.00564	0.00921
100	79 kg	$11,755	$72,816	$53,422	1.0000	1.00000	1.00000

BPA: bypassing agent, Pr.: probability; RR: relative risk

Calculation of Indirect Costs

The 2011 total compensation/hour for civilian workers used by Zhou et al. was $30.11; to adjust for inflation, the equivalent estimate for the year 2017 is $35.64.[94]

Weekly indirect costs for prophylaxis and non-prophylaxis inhibitor patients were then calculated as:

$$((a/b)*c*d)/(365.25/7),$$

where *a* is the annual indirect cost for either prophylaxis or non-prophylaxis severe hemophilia A patients reported in Zhou et al., *b* is the 2011 total compensation/hour, *c* is the 2017 total compensation/hour, and *d* is the calculated ratio (1.8) of inhibitor patients' indirect cost versus the

weighted average indirect cost for severe hemophilia A patients. The derived prophylaxis (emicizumab and BPA) and no prophylaxis indirect costs/week were $361 and $690, respectively.

Table F11. Inflation Index

Consumer Price Index - All Urban Consumers			
Original Data Value			
https://data.bls.gov/timeseries/CUUR0000SAM			
Series Id:	CUUR0000SAM		
Not Seasonally Adjusted			
Area:	**US City Average**		
Item:	**Medical care**		
Base Period:	1982-84=100		
Years:	2011 to 2017		
Year	HALF1 Index	HALF2 Index	
2011	397.7	402.8	
2012	411.9	417.9	
2013	423.2	427.1	
2014	433.3	437.2	
2015	444.7	448.9	
2016	459.1	468.3	
2017	473.7		
Weekly Per Bleed Non-Pharmacy Costs	**Year of Shrestha Study**	**Cost**	**2017 $**
Prophylaxis Age 6-18	2016	$738	$747
Prophylaxis Age 19-44	2016	$4,439	$4,490
Prophylaxis Age >45	2016	$6,612	$6,689
No Prophylaxis Age 6-18	2016	$3,046	$3,081
No Prophylaxis Age 19-44	2016	$4,439	$4,490
No Prophylaxis Age >45	2016	$6,612	$6,689

Appendix G. Summaries of Public Comments Delivered at Public Meeting

Following the Public Meeting, those who delivered public comment were permitted to submit abbreviated summaries of their remarks for inclusion in the final report. Their remarks are included in order of delivery below.

(1) Susan Begelman, MD, F.A.C.C. , Vice President, Rare Disease and Neuroscience Medical Unit, U.S. Medical Affairs; Genentech

Genentech Statement at ICER/CEPAC Hemophilia A (March 29, 2018)

Emicizumab is a transformative, highly efficacious therapy that significantly improves the quality of life for people with hemophilia A and FVIII inhibitors. Genentech agrees with ICER's conclusion that emicizumab is more effective and less costly when compared to prophylactic and on-demand treatment with bypassing agents.

In HAVEN 1, emicizumab-treated patients had an 87% reduction in treated bleeds compared to no prophylaxis. Importantly, 63% of patients had zero treated bleeds compared to 6% for patients with no prophylaxis. Interim results from HAVEN 2 show findings consistent with the annualized bleed rate and reduction in treated bleeds from HAVEN 1.

Patient safety is of utmost importance to Genentech. In HAVEN 1, three cases of thrombotic microangiopathy (TMA) and two cases of thrombotic events (TE) were reported when on average a cumulative amount of more than 100 U/kg/24 hours of aPCC was administered for ≥24 hours while receiving emicizumab prophylaxis. No TMA/TE led to death. No additional serious thrombotic or TMA events have been observed when the dosing guidance of aPCC while on emicizumab was followed. The most common side effects with emicizumab are injection site reactions, headache and arthralgia.

As ICER described, the availability of weekly subcutaneous therapy is less burdensome, likely improves adherence, supports a more active lifestyle, and will broaden career and educational choices for people with hemophilia.

Genentech is committed to generating data to demonstrate the clinical, economic and humanistic value of emicizumab. We thank the hemophilia community in ensuring access to treatments and providing the support to patients.

Conflict of Interest Disclosure*: Susan Begelman is an employee at Genentech.*

(2) Kathleen Gondek, PhD, Global Head of Outcomes Research and Epidemiology, Shire

RE: Shire's Summary for inclusion in the Final Evidence Report Representing the Institute for Clinical and Economic Review (ICER) Evaluation of Emicizumab for Hemophilia A with Inhibitors

Shire would like to inform readers of this Report of the following critical points:

In light of the limited sample size in the HAVEN-1 clinical trial and absence of real-world data for emicizumab, the significant uncertainty in the values estimated in this report should be recognized. In addition, ICER did not have the opportunity to properly evaluate the impact of the recently reported fatal AEs among patients undergoing treatment with emicizumab.

Lack of sufficient comparative evidence precludes conclusive comparative effectiveness analysis and economic modeling. There are only 4 published RCTs for the prophylaxis treatment of hemophilia A with inhibitors[1-4]. Readers should keep in mind that these trials have substantial differences in design, patient population, comparators, endpoints and supportive care, and therefore many assumptions were required for ICER to conduct this comparative clinical effectiveness analysis.

In addition, ICER should have treated aPCC and rFVIIa as separate prophylaxis treatment arms instead of a combined bypassing agent (BPA) comparator arm. Furthermore, we encourage readers to consider the "BPA-favoring scenario" given it is a closer representation of how hemophilia is managed with aPCC and generally how hemophilia impacts patients. Here, the cost of aPCC prophylaxis only in a separate "BPA-favoring scenario" results in an overall 53% lower estimate of BPA costs.

In addition, it is important to re-emphasize that no single hemophilia inhibitor therapy can stop all types of bleeding events in all patients, and therefore clinicians and their patients need to have access to all available therapies.

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4. Oldenburg J, Mahlangu JN, Kim B et al. Emicizumab prophylaxis in hemophilia A with inhibitors. *N Engl J Med*. 2017 Aug 31;377(9):809-818.

Conflict of Interest Disclosure*: Kathleen Gondek is an employee at Shire.*

(3) Johanna Gray, Federal Policy Advisor, National Hemophilia Foundation
Senior Vice President; CRD Associates

National Hemophilia Foundation Statement for ICER Meeting on Emicizumab

The National Hemophilia Foundation (NHF) is the nation's leading advocacy organization working to ensure that individuals affected by hemophilia and related inherited bleeding disorders have access to quality medical care, regardless of financial circumstances or place of residence.

Having a bleeding disorder with an inhibitor has a profound impact on individuals and their families – affecting their daily lives and decisions related to work, school, play, physical activity, family life, and access to insurance and related health care costs. Along with short- and long-term physical effects of internal bleeding and pain that result, psychosocial effects are significant. Affected families face countless sleepless nights, trips to their hemophilia treatment center, emergency rooms, hospital admissions, and a significant disruption to normal family life.

As a result, a number of "other benefits and contextual considerations" are relevant to ICER's review of Emicizumab, including those related to patient outcomes and quality of life; family and caregiver burden and ability to return to work; reduced complexity of administration; and hemophilia with inhibitors being a condition with a significant effect on quality of life and a high lifetime burden of illness.

NHF is pleased that there has been continued investment and additional treatments approved to treat inhibitors. Emicizumab is a critical new option for individuals with inhibitors, but NHF's position is that patients together with their doctors must decide what treatment options are best. Every person's response to treatment is different and a thorough evaluation of risks and benefits and discussion between patient and treater is required.

Conflict of Interest Disclosure: *Consultant for the National Hemophilia Foundation, NHF receives funding from individuals, philanthropic foundations, drug/biotech manufacturers, specialty pharmacies. Organization receives funding from Shire, Novo Nordisk, Genentech.*

(4) Miriam Goldstein
Associate Director, Policy
Hemophilia Federation of America (HFA)

Hemophilia Federation of America is a community-based, grassroots advocacy organization that assists, educates, and advocates for people with bleeding disorders. We appreciate the opportunity to comment.

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

Focusing on "contextual considerations," HFA's remarks on March 29th spotlighted stories we've heard about the "other benefits" that patients have gained, or may look to gain, from use of Emicizumab.

Complexity and patient outcomes: Community members welcome a new treatment option that is effective and easier to use. Patients using Emicizumab reported experiencing longer periods with no bleeds; dramatic reduction in ER visits and hospitalizations; increased physical activity; and reduced use of opioids.

Caregiver and family burden: Families shared stories of exhaustion from keeping up with treatment regimens; depression, anxiety, and isolation – and liberation and improved well-being when more effective treatment became available.

Patient financial burdens remain a concern. Hitting the out-of-pocket maximum – every year, for life, often in January – is enormously consequential. This financial toxicity can impede patient access and adherence to therapy. Plan designs should eliminate excessive cost-sharing for Emicizumab and other hemophilia treatments.

Conclusion. Health plans should cover the full range of inhibitor treatments, at an affordable cost. Patients and doctors should have the right to select the treatment that meets patients' individual goals, physiology, life circumstances, and risk-benefit assessment.

Conflicts of Interest Disclosure*: Employee of HFA, HFA receives funding from individuals, philanthropic foundations, drug/biotech manufacturers, specialty pharmacies. Organization receives funding from Shire, Novo Nordisk, Genentech, Alnylam. Ms. Goldstein is the mother of two adult sons with hemophilia.*

Appendix H. Conflict of Interest Disclosure

(1) Kathleen Gondek, PhD
Global Head of Outcomes Research and Epidemiology
Shire

Conflict of Interest Disclosure*: Kathleen Gondek is an employee at Shire.*

(2) Susan Begelman, MD, F.A.C.C.
Vice President, Rare Disease and Neuroscience Medical Unit, U.S. Medical Affairs
Genentech

Conflict of Interest Disclosure*: Susan Begelman is an employee at Genentech.*

(3) Steven Pipe, MD
Professor of Pediatrics and Communicable Diseases; Professor of Pathology
University of Michigan

Conflict of Interest Disclosure: *Dr. Pipe has disclosed receipt of consulting fees in excess of $5,000 from the following life sciences companies: Bayer, BioMarin, Bioverativ, CSL Behring, Novo Nordisk, Pfizer, Roche, Shire, uniQure. In addition, Shire has sponsored basic research conducted by Dr. Pipe.*

(4) Margaret V. Ragni, MD, MPH
Professor of Medicine, Division of Hematology/Oncology, University of Pittsburgh; Director, Hemophilia Center of Western PA

Conflict of Interest Disclosure: *No relevant conflicts of interest to disclose, defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers*

(5) Sonji Wilkes

- Sonji Wilkes is the mother of a teenage son who has severe hemophilia A and inhibitors.

- Sonji is employed by Hemophilia Federation of America (HFA) as an associate director for advocacy. HFA is a national nonprofit organization that assists, educates, and advocates for the bleeding disorders community. Organized as a community-focused federation, HFA comprises 45 state and local organizations. HFA receives funding in the form of donations from individuals, philanthropic foundations, drug/biotech manufacturers, and specialty pharmacies; a cooperative grant from the US Centers for Disease Control; an engagement

award from the Patient-Centered Outcomes Research Institute; and sponsorship income from a symposium it holds annually. A list of corporate supporters can be found at http://www.hemophiliafed.org/our-role-and-programs/what-is-hfa/corporate-supporters/.

(6) Mark W. Skinner, JD

President and CEO, Institute for Policy Advancement Ltd.; Past President (2004-2012), World Federation of Hemophilia; President, World Federation of Hemophilia USA

Conflict of Interest Disclosure: *Mr. Skinner has disclosed the following relationships:*

- *Honoraria > $5,000: Mr. Skinner has received honoraria for educational presentations and advisory board participation with F. Hoffman-La Roche, Bayer Healthcare, and the Blue Cross Blue Shield Medical Advisory Panel.*
- *Equity Interests > $10,000: Mr. Skinner's household has equity interests in the following companies: CVS, Foundation Medicine, Illumina, Intuitive Surgical, Merck, Novartis, Regeneron. These holdings are managed by a financial advisor with instructions not to invest in companies with a known interest in therapies for bleeding disorders.*
- *Positions: Mr. Skinner is the president of World Federation of Hemophilia USA, which receives product and monetary donations for a humanitarian aid program, serves as a consultant for the US National Hemophilia Foundation, and is a member of the NHF Scientific Advisory Council.*
- *Research: Mr. Skinner is a Principal investigator for the Patient-Reported Outcomes and Burdens and Experiences (PROBE) study, which is funded with grant support from Baxalta (part of Shire), Bayer, Bioverativ, CSL Behring, Novo Nordisk, Roche, Sobi. The PROBE study is an independent, investigator-led research project led by patients and patient advocacy organizations.*

Personal: Mr. Skinner is a person with severe hemophilia A.

(7) Tom Kowalski, RPH
Clinical Pharmacy Director
Blue Cross Blue Shield Massachusetts

Conflict of Interest Disclosure: Tom is an employee of Blue Cross Blue Shield Massachusetts.

(8) Herman Kranc, RPH
Manager-Integrated Care
Connecticut Department of Social Services

Conflict of Interest Disclosure: Herman is an employee of Connecticut Department of Social Services, and manages their pharmacy program.