Gene Therapy for Hemophilia B and An Update on Gene Therapy for Hemophilia A: Effectiveness and Value

Final Evidence Report

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Prepared for

July 26, 2024: Per ICER's guidelines on the acceptance and use of "In-Confidence" data from manufacturers of pharmaceuticals, academic-in-confidence data that was redacted in the report has been unmasked after 18 months following the date of the public ICER meeting.

July 26, 2024: New evidence regarding treatments and therapies gets published on an ongoing basis. ICER reached out to key stakeholders included in this review 18 months after the publication of this report giving them an opportunity to submit public comments regarding new relevant data or information on coverage that they wish to highlight. Their statements can be found here. ICER has launched ICER Analytics to provide stakeholders an opportunity to work directly with ICER models and examine how changes in parameters would affect results. You can learn more about ICER Analytics here.

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None of the above authors disclosed any conflicts of interest defined as more than $10,000 in health care company stock or more than $5,000 in honoraria or consultancies relevant to this report during the previous year from health care manufacturers or insurers.

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Jeffrey A. Tice served as the lead author for the Report. Belen Herce-Hagiwara and Shahariar Mohammed Fahim led the systematic review and authorship of the comparative clinical effectiveness section of this Report in collaboration with Foluso Agboola. Surrey Walton developed the cost-effectiveness model and authored the corresponding sections of the Report with assistance from Jyotirmoy Sarker. Ashton Moradi provided consultation on the cost-effectiveness analyses and conducted analyses for the budget impact model. David M. Rind and Steven D. Pearson provided methodologic guidance on the clinical and economic evaluations. We would also like to thank Monica Frederick, Yasmine Kayali, Liis Shea, and Janet Chu for their contributions to this Report.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. Through all its work, ICER seeks to help create a future in which collaborative efforts to move evidence into action provide the foundation for a more effective, efficient, and just health care system. More information about ICER is available at https://icer.org/.

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For drug topics, in addition to receiving recommendations from the public, ICER scans publicly available information and also benefits from a collaboration with IPD Analytics, an independent organization that performs analyses of the emerging drug pipeline for a diverse group of industry stakeholders, including payers, pharmaceutical manufacturers, providers, and wholesalers. IPD provides a tailored report on the drug pipeline on a courtesy basis to ICER but does not prioritize topics for specific ICER assessments.

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The CTAF Panel is an independent committee of medical evidence experts from across California, with a mix of practicing clinicians, methodologists, and leaders in patient engagement and advocacy. All Panel members meet strict conflict of interest guidelines and are convened to discuss the evidence summarized in ICER reports and vote on the comparative clinical effectiveness and value of medical interventions. More information about CTAF is available at https://icer.org/who-we-are/people/independent-appraisal-committees/ctaf.

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.

The economic models used in ICER reports are intended to compare the clinical outcomes, expected costs, and cost-effectiveness of different care pathways for broad groups of patients. Model results therefore represent average findings across patients and should not be presumed to represent the clinical or cost outcomes for any specific patient. In addition, data inputs to ICER models often come from clinical trials; patients in these trials may differ in real-world practice settings.

In the development of this report, ICER's researchers consulted with several clinical experts, patients, manufacturers, and other stakeholders. The following experts provided input that helped guide the ICER team as we shaped our scope and report. It is possible that expert reviewers may not have had the opportunity to review all portions of this report. None of these individuals is responsible for the final contents of this report, nor should it be assumed that they support any part of it. The report should be viewed as attributable solely to the ICER team and its affiliated researchers.

For a complete list of stakeholders from whom we requested input, please visit: https://icer.org/assessment/hemophilia-a-and-b-2022/

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Table of Contents

List of Acronyms and Abbreviations Used in this Report

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

Executive Summary

Hemophilia A and B are conditions of increased tendency to bleed due to inherited deficiencies of factor VIII and factor IX, respectively, which disrupt the clotting cascade (Figure 1). Both have X-linked recessive inheritance, and so predominately affect males. Approximately 76% of all male hemophilia patients in the US have hemophilia A and the remainder have hemophilia B.[1] The exact prevalence of hemophilia in the United States (US) is not known, but is estimated to be around 30,000 to 33,000.[1]

Patients with both hemophilia A and B, 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 leads to substantial disability from pain and loss of mobility.[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 have typically administered factor concentrate intravenously several times each week. Several factor preparations are available for prophylaxis, some prepared from human plasma, some prepared using recombinant technology including some with modifications to extend the half-life of the therapy. Many patients with hemophilia A now use a non-factor replacement therapy, emicizumab, a monoclonal antibody that can be administered monthly by subcutaneous injection, for prophylaxis in preference to factor VIII; no similar prophylaxis is currently available for hemophilia B.

Valoctocogene roxaparvovec (Valrox) is an adeno-associated virus serotype 5 (AAV5) mediated gene therapy for hemophilia A.[5] It is a one-time infusion of a B-domain-deleted factor VIII gene to cells in the liver, resulting in production of an active variant of factor VIII.

Etranacogene dezaparvovec (Etranadez) is an AAV5-mediated gene therapy for hemophilia B. It is a one-time infusion of the highly active Padua variant of the gene for factor IX to cells in the liver, resulting in production of an active variant of factor IX.

Etranacogene Dezaparvovec Compared with Factor IX Prophylaxis in Adults with Hemophilia B

Patients treated with etranacogene dezaparvovec had an 80% reduction in treated joint bleeds and similar reductions in other bleeds when compared with their bleeding rates on factor prophylaxis prior to gene therapy. No patients successfully treated with etranacogene dezaparvovec had to go back on factor prophylaxis during the first 18 months of therapy. It is not yet clear that the initial increase in factor IX levels will be maintained for decades, though the results are encouraging. Finally, the reduction in burden of therapy – no longer needing weekly or more frequent IX factor therapy is a major benefit for patients. Because of the uncontrolled study design, small numbers of

patients studied and relatively short follow-up, there is still considerable uncertainty about the long-term net benefits of etranacogene dezaparvovec compared with factor IX prophylaxis. In particular, there are uncertainties about the long-term impact of the therapy on liver function and the risk for hepatocellular carcinoma. We conclude that there is moderate certainty of a small or substantial health benefit with high certainty of at least a small net health benefit (B+) for etranacogene dezaparvovec compared with factor IX prophylaxis.

Valoctocogene Roxaparvovec Compared with Emicizumab in Adults with Hemophilia A

There is no direct evidence comparing valoctocogene roxaparvovec with emicizumab. Indirect evidence suggests that the short-term reduction in bleeding rates with valoctocogene roxaparvovec compared with factor prophylaxis are at least as great as that observed with emicizumab compared with factor prophylaxis. However, differences in the patient populations studied in the trials could be responsible for the observed benefits. Furthermore, there are clear initial adverse events with valoctocogene roxaparvovec (high risk of elevated liver enzymes requiring prolonged corticosteroid therapy). Because of the uncontrolled study design, small numbers of patients studied and relatively short follow-up, there is still considerable uncertainty about the long-term net benefits of valoctocogene roxaparvovec compared with emicizumab. In particular, there are uncertainties about the long-term impact of the therapy on liver function and the risk for hepatocellular carcinoma. Finally, as factor levels have been observed to decline over time, the benefits of valoctocogene roxaparvovec could be relatively short-lived. The lack of direct data comparing the two therapies, the small number of treated patients, and the modest long-term follow-up leave considerable uncertainty about the net health benefits. Thus, we conclude that there is low certainty about the net health benefit (I) for valoctocogene roxaparvovec compared with emicizumab.

Valoctocogene Roxaparvovec Compared with Factor VIII Prophylaxis in Adults with Hemophilia A

In ICER's 2020 review of valoctocogene roxaparvovec compared with factor VIII prophylaxis, we gave valoctocogene roxaparvovec a promising, but inconclusive (P/I) rating. It is clear that some patients get a significant benefit, while others get minimal to no benefit from valoctocogene roxaparvovec. Because of the uncontrolled study design, small numbers of patients studied and relatively short follow-up, there is still considerable uncertainty about the long-term net benefits of valoctocogene roxaparvovec compared with factor VIII prophylaxis. In particular, there are uncertainties about the long-term impact of the therapy on liver function and the risk for hepatocellular carcinoma. Finally, as factor levels have been observed to decline over time, the benefits of valoctocogene roxaparvovec could be relatively short-lived. Thus, we conclude that there is moderate certainty of a comparable, small, or substantial health benefit with high certainty of at least a comparable net health benefit (C++) for valoctocogene roxaparvovec compared with factor VIII prophylaxis.

Table ES1. Evidence Ratings

Treatment	Comparator	Evidence Rating
Adults with Hemophilia B who Require Factor IX Prophylaxis		
Etranacogene Dezaparvovec	Factor Prophylaxis	B+
Adults with Hemophilia A who Require Factor VIII Prophylaxis		
Valoctocogene Roxaparvovec	Emicizumab	I
Valoctocogene Roxaparvovec	Factor Prophylaxis	C++

We conducted an economic evaluation of etranacogene dezaparvovec for the treatment of hemophilia B patients without inhibitors compared with prophylactic treatment. We also updated our economic evaluation of valoctocogene roxaparvovec for the treatment of hemophilia A patients without inhibitors compared with emicizumab.

Lifetime costs for the gene therapies as well as for the comparators in each model were substantial. Using a traditional analysis that includes the full cost offset of standard of care, we found that both etranacogene dezaparvovec at a price of $3,500,000 and valoctocogene roxaparvovec at a placeholder price of $2,500,000 were dominant treatments with substantial cost savings along with projected gains in quality adjusted life years. These findings were robust to numerous sensitivity analyses and scenario analyses.

As discussed in greater detail in Section 6, ICER has concluded that in a situation where a large percentage of the traditional Health Benefit Price Benchmark (HBPB) comes from cost offsets of therapies that, themselves, have prices that are not believed to be aligned with benefits to patients, ICER will present ranges from shared savings calculations as the most policy-relevant HBPBs. We calculate that more than 99% of the traditional HBPB results for both valoctocogene roxaparvovec and etranacogene dezaparvovec come from offsetting the price of prophylaxis with existing agents that cost far in excess of $300,000 per year.

In shared savings scenarios that use an annual cap of $150,000 on cost offsets, for valoctocogene roxaparvovec the HBPB is $1.96 million to $1.96 million and for etranacogene dezaparvovec the HBPB is $2.93 million to $2.96 million.

Appraisal committee votes on questions of comparative effectiveness and value, along with key policy recommendations regarding pricing, and future research are included in the main report. Several key themes are highlighted below.

- The value of high-impact single and short-term therapies should not be determined exclusively by estimates of long-term cost offsets, particularly when the existing standard of care is acknowledged to be priced significantly higher than reasonable cost-effective levels.

- Payers should work with manufacturers to develop and implement outcomes-based agreements to address the uncertainty and the high cost of gene therapies for hemophilia.

- At least one national payer has suggested to patient representatives that step therapy with emicizumab is being considered prior to provision of coverage for Roctavian. Clinical experts and patient experts view this approach as lacking any clinical justification and appears to be only a method for trying to avoid the high one-time fee for gene therapy while assuming that patients may switch insurers before the cost-saving potential of gene therapy is fully realized. In short, step therapy does not appear to be a reasonable consideration for this treatment.

1. Background

ICER reviewed valoctocogene roxaparvovec for hemophilia A in 2020 (Valoctocogene roxaparvovec and Emicizumab for Hemophilia A without Inhibitors: Effectiveness and Value). Much of the background information in this draft scoping document is updated from that report with the addition of contextual information for hemophilia B. In this review, the two interventions will be considered separately as if we were performing two independent reviews in two different populations.

Hemophilia A and B are conditions of increased tendency to bleed due to inherited deficiencies of factor VIII and factor IX, respectively, which disrupt the clotting cascade (Figure 1). Both have X-linked recessive inheritance, and so predominately affect males. Approximately 76% of all male hemophilia patients in the US have hemophilia A and the remainder have hemophilia B.[1] The exact prevalence of hemophilia in the United States (US) is not known, but is estimated to be around 30,000 to 33,000.[1]

Patients with both hemophilia A and B, 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 leads to substantial disability from pain and loss of mobility.[2] Hemarthroses cause ongoing joint inflammation and damage and also increase the likelihood of further bleeding into the same joint.

The severity of hemophilia A and B has generally been defined by factor levels (the percentage of factor VIII or IX that a patient has).[6] Severity based on factor levels does not perfectly correlate with any individual's clinical severity, but no other classification system is widely accepted.[7] Using factor level classifications, severe disease is defined by factor levels below 1% of normal.[6] 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.[8] Patients with moderate disease (factor 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 levels between 5% to 40% of normal) typically have bleeding after procedures such as tooth extractions or surgery, or after significant injuries.[3]

To reduce the risk of bleeding, patients with severe hemophilia have typically administered factor concentrate intravenously several times each week. The use of factor concentrates both as treatment and prophylaxis, has dramatically altered the management and clinical course of patients with hemophilia. However, prophylaxis with factor replacement is burdensome and does not maintain patients at normal levels of factor. Several factor preparations are available for prophylaxis, some prepared from human plasma, some prepared using recombinant technology including some with modifications to extend the half-life of the therapy. Many patients with

hemophilia A now use emicizumab, a monoclonal antibody that can be administered monthly by subcutaneous injection, for prophylaxis in preference to factor VIII; no similar treatment is currently available for hemophilia B.

Valoctocogene roxaparvovec is an adeno-associated virus serotype 5 (AAV5) mediated gene therapy for hemophilia A.[5] It delivers a B-domain-deleted factor VIII gene to cells in the liver, resulting in production of an active variant of factor VIII. In August 2020, BioMarin Pharmaceutical received a complete response letter from the FDA changing the primary endpoint of the pivotal trial to the annualized bleeding rate at two years in the Phase 3 trial. The last patient in the trial completed two years of follow-up in November 2021. The FDA accepted BioMarin's biologic license application for valoctocogene roxaparvovec on October 13, 2022 with a PDUFA date of March 31, 2023. In addition, valoctocogene roxaparvovec received conditional market authorization with requirements for additional monitoring for the treatment of severe hemophilia A adults on August 24, 2022 by the European Commission.

Etranacogene dezaparvovec is an AAV5-mediated gene therapy for hemophilia B. It delivers the highly active Padua variant of the gene for factor IX to cells in the liver, resulting in production of an active variant of factor IX. The FDA recently approved CSL Behring's biologic license application for etranacogene dezaparvovec as the first therapy to treat people with hemophilia B at 3.5 million per dose.

2. Patient and Caregiver Perspectives

One overarching theme we heard was that the outcome that matters most to patients is participation. This includes participation in family life, recreational activities, school activities, and work activities without restriction. This reflects both the impact of bleeding events on time away from activities and the fear of bleeding events limiting participation. For adults whom we spoke with, another common theme was the impact of permanent joint damage from prior bleeds on their quality of life.

Bleeding events and joint pain are important, but the sequelae of those outcomes are equally important. Living with uncertainty and chronic pain can lead to significant mental health issues (anxiety, depression, fatigue, substance use issues). The psychosocial impact of hemophilia on patients and their caregivers is enormous. This applies to all patients living with hemophilia, not just those with severe disease. All patients with hemophilia modify their lifestyles to reduce the risk of serious bleeding and this impacts their quality of life.

There are issues with the use of current quality of life measures in hemophilia. The coreHEM measures are good but miss some aspects of quality of life in patients with hemophilia. There can be a disability paradox in hemophilia: patients living with hemophilia who report that their health status is better than that of the average population. If population-based measures are used, rather than those directly assessed in patients with hemophilia, the quality of life for patients living with hemophilia may be misrepresented.

Intravenous infusions are an enormous burden to patients and to their caregivers. A huge weight would be lifted if regular factor infusions were no longer required. However, there are also significant burdens associated with gene therapy. The frequent laboratory monitoring and life changes (use of barrier contraception until viral vector is cleared from the semen, abstinence from alcohol for a year) also impact patients' quality of life.

Patients expressed frustrations with access to care – particularly access to specialists who understood how to care for patients with hemophilia. This sometimes impacts decisions about where patients and their caregivers live.

We also heard that patients are reluctant to try new therapies. The hemophilia community has been harmed in the past by heralded new therapies that turned out to be disastrous, particularly those that resulted in infections with HIV, hepatitis B and hepatitis C. Once they achieve stability with a specific therapy, they are loathe to change even if there are theoretical benefits to a novel therapy (fewer infusions, subcutaneous rather than IV administration). The community understands the need for substantial numbers of patients followed for a long time to ensure that the benefits outweigh potential unknown harms. They are particularly concerned about the

durability of gene therapy and potentially wasting what could be one shot at gene therapy on an approach that ends up not having lifetime efficacy. They are also concerned about the potential for thrombotic events.

Finally, the financial toxicity associated with the high costs of most of the therapies for hemophilia impacts fair and equitable access to appropriate treatment for patients. Insurance mechanisms in response to high costs, such as cost-sharing and step therapy, directly impact patients.

On the flip side, we heard repeatedly about the positive impact of the hemophilia community on their lives. Patients learn practical tips from each other and are pushed by older people living with hemophilia to not limit their aspirations in life. In particular, patients spoke glowingly of what they gained from participating in camps for people with bleeding disorders and the long-term friendships and support that grew out of those experiences.

As described in our last report, 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 (sports, mountain climbing, boxing, running, acrobatics, football, etc.)
- 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. Over time, joint injury from bleeding can further restrict patient activities due to pain, disability, reduced range of motion, and in some cases, may require joint replacement surgery. These same joint injuries can eventually limit the ability of patients to care for themselves, as arthritis caused by bleeds may prevent patients from self-administering intravenous infusions.

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

There is a substantial time burden associated with prophylaxis with factor therapy, as patients who require multiple doses per week must find time for infusions; this can be particularly challenging for caregivers of young and school-aged children, as infusion would need to take place before the

school day, and the parent/caregiver's workday, begins. Caregivers of patients who receive infusions through a port must also carefully monitor the port for infection, and such devices may also need to be periodically replaced, and, if they become infected, may require hospitalization for antibiotic treatment, adding to financial and time burdens.

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

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

We also heard concerns from patients and patient groups that they had struggled to get insurance coverage for dosing regimens of factor therapy that maintain trough levels high enough to adequately control risk of bleeding.

Patients also raised the concern that if they received gene therapy, they might not be able to receive insurance authorization for factor prophylaxis if the gene therapy was either not successful initially or if factor levels fell too low to be effective in the future for spontaneous, traumatic, or surgical bleeding.

While it may not be immediately available to all, given the enormous variability in health care coverage in the United States and the significant financial impact (work, career, educational opportunities) hemophilia has on people with hemophilia and their families, a durable transformative therapy could have a generational impact that breaks the cycle of economic disadvantage experienced by many in the hemophilia community.

3. Comparative Clinical Effectiveness

3.1. Methods Overview

Procedures for the systematic literature review (SLR) assessing the evidence on etranacogene dezaparvovec and valoctocogene roxaparvovec for the treatment of hemophilia B and A, respectively, are described in Supplement Section D1.

Scope of Review

Hemophilia B

We reviewed the clinical effectiveness of etranacogene dezaparvovec compared with prophylaxis using factor IX preparations in adults eligible for factor prophylaxis.

Hemophilia A

We updated our prior review of the clinical effectiveness of valoctocogene roxaparvovec in adults eligible for factor prophylaxis compared with both factor VIII prophylaxis and emicizumab. In ICER's 2020 review, the evidence on the success rate, initial levels of factor achieved, and duration of benefit were limited because the valoctocogene roxaparvovec Phase 3 trial (GENEr8-1) data had only short follow-up data available for review.

For both patient populations, we searched for evidence on patient-important outcomes including patient-reported quality of life, bleeding rates, treated bleeding events, pain, mental health status, and adverse events as well as factor activity levels which are important intermediate outcomes for gene therapy. The full scope of this review is detailed in the Supplement.

Evidence Base

Hemophilia B

Our search identified a total of 6 references arising from two trials of etranacogene dezaparvovec. Additional details about the study designs of these two trials can be found in the Supplement Table D6.[9-16]

The key trial for etranacogene dezaparvovec is the Phase 3 Hope-B trial that includes 54 patients.[9-12] In addition, the evidence to inform our assessment of etranacogene dezaparvovec included results from a Phase 2b trial with three patients only. Both studies are single-arm trials that included adult males with moderately severe to severe hemophilia B. The annualized bleeding rate at 52 weeks was assessed as a primary outcome in the HOPE-B trial while factor IX activity was considered as a

primary outcome for the Phase 2b trial. The patients in these two trials received a single dose of etranacogene dezaparvovec 2×10^13 gc/kg.

Hemophilia A

The evidence informing this section of the review was derived from two valoctocogene roxaparvovec trials, one emicizumab trial, and one emicizumab observational study. A total of 7 references were retrieved for valoctocogene roxaparvovec[17-20] and 6 references[21-26] were obtained for emicizumab. A total of 7 references were retrieved for valoctocogene roxaparvovec[17-20] and 6 references[21,2223-26] were obtained for emicizumab. Detailed description of the study designs of these trials and observational study can be found in Supplement D2.

For severe hemophilia A patients, the key trial of valoctocogene roxaparvovec is the Phase 3 GENEr8-1 trial which included 134 patients and has 2-year follow-up.[17] The second small trial is the Phase 1/2 BMN 270-201 with only 7 patients, but had follow-up through 6 years.[27] Both trials were included in the previous ICER 2020 review, but we only had limited interim data on the GENEr8-1 trial with 16 patients who had reached 26 weeks in the previous review. The GENEr8-1 trial assessed factor VIII activity as a primary outcome while the Phase 1/2 trial assessed treatment-related adverse events. Both factor VIII usage and annualized bleeding rate were assessed as secondary outcomes in these two trials. Although several patients in the Phase 1/2 trial received a single dose of 4×10^13 vg/kg, we only summarized results for severe hemophilia A patients who received a single infusion of 6×10^13 vg/kg in these two trials of valoctocogene roxaparvovec. In contrast, the key trial of emicizumab is the Phase 3 HAVEN-3 trial which included patients aged 12 years old or above with severe hemophilia A without inhibitors and had 24 weeks follow-up.[22] In this HAVEN-3 trial, we are only focusing on the patients who received factor VIII prophylaxis prior to getting 1.5 mg/kg emicizumab every week. A total of 48 patients were included in this group and labeled as group D in the HAVEN-3 trial. The primary outcome was annualized bleeding rate and the secondary outcomes included both HRQoL and safety measurements.

Table 3.1 Overview of Key Studies

Drug	Trial & Design	Population	Outcomes	Longest Follow-Up
Hemophilia B				
Etranacogene Dezaparvovec	HOPE-B Phase 3 (N=54)	Adult males with moderately severe to severe hemophilia B	Primary - ABR [52 weeks] Secondary - FIX activity [18 months] - FIX usage - Adverse events	24 months
	AMT-061-01 Phase 2b (N=3)	Adult males with moderately severe to severe hemophilia B	Primary - FIX activity [from 6 weeks] Secondary - Factor IX usage [30 months] - ABR [30 months] - Adverse events [5 years]	3 years
Hemophilia A				
Valoctocogene Roxaparvovec	GENEr8-1 Phase 3 (N=134)	Adult males with severe hemophilia A	Primary - Factor VIII activity [52 weeks] Secondary - Factor VIII usage [52 weeks] - ABR [52 weeks]	2 years
	BMN 270-201 Phase 1/2 (N=7)*	Adult males with severe hemophilia A	Primary - Treatment-related adverse events [85 months] - Dose Secondary - FVIII usage [85 months] - ABR [85 months]	6 years
Emicizumab	HAVEN 3 Phase 3 Group D (N=48)	Ages 12+ years with severe hemophilia A without inhibitors	Primary - ABR for treated bleeds [24 weeks] Secondary - ABR for all bleeds, treated joint and spontaneous bleeds [24 weeks] - HRQoL - Safety [up to 2.5 years]	24 weeks

* 15 patients total infused, but only seven infused with the same dose as in the Phase 3 trial

ABR: annualized bleeding rate, FIX: factor IX, FVIII: factor VIII, N: total number

3.2. Results

Clinical Benefits

Gene Therapy for Adults with Hemophilia B Without Inhibitors

The primary benefit from gene therapy is a reduction in ABR over time. Bleeding into joints is particularly important as repeated bleeding events lead to progressive joint damage and thus progressive disability and pain. The bleeding rates reported in the HOPE-B trial (Table 3.2 below)

reflect the change from baseline ABR during the 6 month run in phase when patients were on factor IX prophylaxis.[9] The bleeding rates reported in the HOPE-B trial (Table 3.2 below) reflect the change from baseline ABR during the 6 month run in phase when patients were on factor IX prophylaxis.[9] All of the reductions were clinically and statistically significant. Because this is not a randomized comparison, there is concern for possible selection bias. In particular, patients choosing gene therapy may have had higher ABRs at baseline than other patients on prophylaxis. However, this does not appear to be an issue as the ABRs observed during the run-in phase were comparable to those reported in a recent systematic review of ABRs for people with hemophilia B on factor prophylaxis (Supplement Table D10).[28]

Table 3.2. Annualized Bleeding Rates in the HOPE-B Trial

Bleed Type	Relative Risk Reduction*
Treated Joint Bleeds	80%
Treated Bleeds	77%
All Bleeds	64%

* Comparing annualized bleeding rate following gene therapy to the annualized bleeding rate for the same patients on factor prophylaxis prior to gene therapy

A secondary, but important benefit of gene therapy is freedom from the need to inject factor IX into a vein one or more times a week. In the HOPE-B trial, 96% of patients were able to discontinue factor IX prophylaxis.[9] Of the two non-responders, one had high antibody titers to the adeno-associated virus vector at baseline and the second only received 10% of the target dose. There are concerns about the variability in the response to gene therapy and the duration of benefit. As can be seen in Table 3.3, the factor levels in the blood six months after gene therapy varied from 8.2 to 97.1 IU/dL, representing a broad range of patient response. None of the responders restarted factor prophylaxis during the 18 months of the trial, but the long-term outcomes remain to be seen. The levels at 18 months were slightly lower than at 6 and 12 months. It remains to be seen if there is a downward trend over many years of follow-up or if the factor expression levels remain stable. The Phase 2b study with only 3 patients reported the highest mean factor IX level at 30 months, but the lowest at 36 months (Supplement Table D9).[29] In a Phase 1/2 study using wild-type gene for factor IX rather than the Padua variant, factor levels appeared to be stable in 10 patients through 5 years.[16]).

Table 3.3. Factor Activity Over Time in the HOPE-B Trial

	Month		
	6	12	18
Factor Activity, IU/dL Mean (range)	39.0 (8.2-97.1)	41.5 (5.9-113)	36.9 (4.5-122.9)

These clinical benefits translated into an improvement in quality of life on the Haem-A-Qol questionnaire (total score improvement of 5.5 points at one year, p<0.0001).9 Additional details

about the quality of life subscales and other quality of life measures can be found in Supplement Table D13.

Gene Therapy or Emicizumab for Adults with Hemophilia A Without Inhibitors

Valoctocogene Roxaparvovec

As in people with hemophilia B, the primary benefit from gene therapy for people with hemophilia A is a reduction in the ABR over time. The bleeding rates reported in the GENEr8-1 trial (Table 3.4 below) reflect the change from baseline ABR during the 6 month run in phase when patients were on factor VIII prophylaxis.[17] All of the reductions were clinically and statistically significant.

Table 3.4. Annualized Bleeding Rates in the GENEr8-1 Trial

Bleed Type	Relative Risk Reduction*
Treated Joint Bleeds	84%
Treated Bleeds	85%
All Bleeds	NR

* Comparing annualized bleeding rate following gene therapy to the annualized bleeding rate for the same patients on factor prophylaxis prior to gene therapy

A secondary, but important benefit of gene therapy is freedom from the need to inject factor VIII into a vein one or more times a week. In the GENEr8-1 trial, 16 participants (12.1%) had factor VIII levels < 5 IU/dL and 12 participants (9.1%) had levels < 3 IU/dL.[17] In the 2 year follow-up reported in July 2022, 5 of 31 patients with factor VIII level < 5 IU/dL had resumed prophylaxis and 1 participant with a factor VIII level > 5 IU/dL had resumed prophylaxis.[18] There are concerns about the variability in the response to gene therapy and the duration of benefit. As can be seen in Table 3.5, the factor levels in the blood six months after gene therapy varied widely with the interquartile range going from 11.2 to 55 IU/dL with 12 patients as noted above having undetectable factor VIII. The factor VIII levels appear to decline markedly over time (Table 3.5). Factor VIII levels continued to decline in the small subset of patients with at least 3 years follow-up (n=7) in the GENEr8-1 trial[17] and in the 7 patients with 5 years follow-up in the phase 1/2 trial (Supplement Table D15).[30]

Table 3.5. Factor Activity Over Time in the GENEr8-1 Trial

	Month	
	12	24
Factor Activity, IU/dL Mean (interquartile range)	42.2 (11.2-55.0)	24.2 (6.4-28.6)

Treatment with valoctocogene roxaparvovec resulted in an improvement in quality of life on the Haemo-Qol-A questionnaire (total score improvement of 6.4 points at one year, p<0.0001).20 Additional details about the quality of life subscales and other quality of life measures can be found in Supplement Table D20.

Emicizumab

Emicizumab was reviewed in detail in ICER's 2020 review of therapies for hemophilia A.[31] In this review, we are highlighting Group D in the report of the pivotal HAVEN 3 trial[22] because the investigators collected bleeding rates for patients on an adequate dose of factor VIII for at least 24 weeks prior to starting emicizumab in adult patients without inhibitors. This allows for pre-post treatment comparisons of bleeding rates similar to the analyses done for valoctocogene roxaparvovec in the GENEr8-1 trial.

Compared with the period on prophylaxis, patients on emicizumab had a 68% reduction in treated bleeds and a 63% reduction in all bleeds. The relative rates of treated joint bleeds were not reported. A real world observational study of emicizumab in the United Kingdom confirmed prolonged, stable reductions in bleeding rates.[26]

Table 3.6. Annualized Bleeding Rates in Group D of the HAVEN 3 Trial

Bleed Type	Relative Risk Reduction*
Treated Joint Bleeds	NR
Treated Bleeds	68%
All Bleeds	63%

* Comparing annualized bleeding rate on emicizumab to the annualized bleeding rate for the same patients on factor prophylaxis prior to starting emicizumab

Haem-A-Qol results were not reported for Group D, but overall in the HAVEN 3 trial, the total score improved by 11.8 points[25] and 98% of patients in group D preferred emicizumab to factor VIII prophylaxis.

Harms

Gene Therapy for Adults with Hemophilia B Without Inhibitors

Etranacogene Dezaparvovec

The most significant harm following treatment with etranacogene dezaparvovec was liver enzyme elevation, all of which required treatment with corticosteroids according to the study protocol (n=9, 16.7%).9 The mean duration of corticosteroid treatment was 79 days and specific complications of corticosteroid therapy were not reported. Common adverse events included headaches (n=8), influenza-like illness (n=7), and infusion-related reactions (n=7) (see Supplement Table D12 for additional details). One patient died from urosepsis and another patient developed hepatocellular cancer, but both were assessed as not related to the study treatment.

Gene Therapy or Emicizumab for Adults with Hemophilia A Without Inhibitors

Valoctocogene Roxaparvovec

The most significant harm following treatment with valoctocogene roxaparvovec was liver enzyme elevation requiring treatment with corticosteroids (n=106, 79.1%).[18] The mean duration of corticosteroid treatment was 34.7 weeks. Adverse effects due to corticosteroids included acne, insomnia, Cushing's syndrome, and weight gain including 3 serious adverse events (2.2%). A total of 17.9% of participants had serious adverse events. Common adverse events included headaches (41%), nausea (38%), arthralgia (40%) and fatigue (30%)[18] (see Supplement Table D19 for additional details). In the phase 1/2 trial there was one grade 2 acinar cell carcinoma of the parotid gland assessed as not related to valoctocogene roxaparvovec by vector integration site analyses.[30] In the phase 3 GENEr8-1 trial, one patient was diagnosed with acute lymphoblastic leukemia 3 years after receiving gene therapy, though not thought to be due to the therapy.[32]

Emicizumab

The adverse events for emicizumab in the HAVEN 3 trial are summarized in Supplemental Table D19. In brief, in Group D 12.7% of patients experienced serious adverse events and there were no deaths. Common adverse events included injection site reactions (32%), arthralgias (22%), nasopharyngitis (16%), and headaches (13%).[22]

Uncertainty and Controversies

Etranacogene Dezaparvovec for People with Hemophilia B

There are several important limitations to the evidence base for etranacogene dezaparvovec. First, all of the studies use a single arm design, so the findings might be in part due to selection bias and confounding. In addition, the number of patients treated is quite small, so there is significant uncertainty around the estimates for the outcomes, particularly for follow-up beyond 18 months. It is not yet clear whether etranacogene dezaparvovec will have the same long-term decline in factor levels that has been observed with valoctocogene roxaparvovec, though the decline appears to be more gradual, if it occurs at all. Finally, the long-term impact of the therapy on liver function and the potential for oncogenesis remain a concern.

Valoctocogene Roxaparvovec for People with Hemophilia A

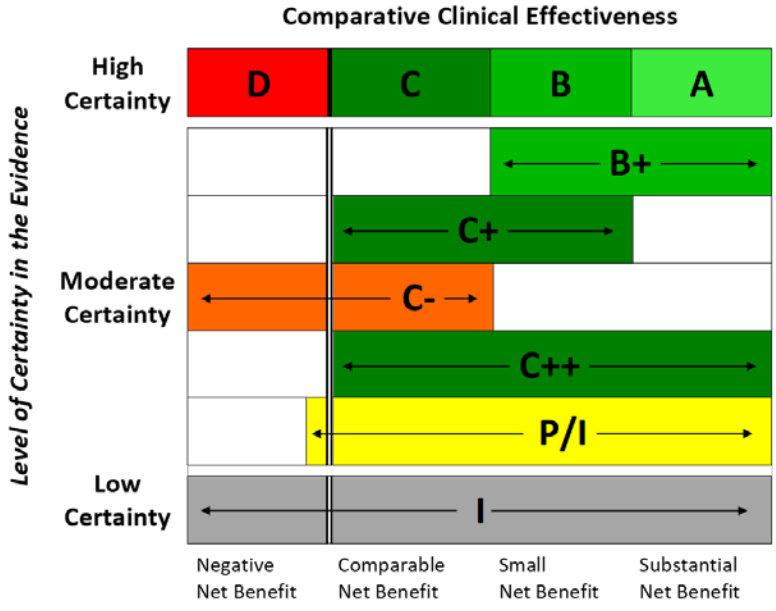
There are similar concerns about the evidence base for valoctocogene roxaparvovec as there were when ICER last reviewed the therapy. As with etranacogene dezaparvovec, the trials use a single arm design and are relatively small, particularly when looking at follow-up beyond two years. The data from the GENEr8-1 trial are now mature and demonstrate short term benefits, but also confirm a significant decline in factor VIII levels over time. Valoctocogene roxaparvovec is unlikely to represent a long-term cure for hemophilia A. Finally, the long-term impact of the therapy on liver function and the potential for oncogenesis remain a concern.

There are also no head-to-head data comparing valoctocogene roxaparvovec to emicizumab, which is gradually replacing factor VIII prophylaxis as the standard therapy for treating children and adults with hemophilia A. Thus, it is challenging to assess the comparative effectiveness of these two therapies in adults.

3.3. Summary and Comment

An explanation of the ICER Evidence Rating Matrix (Figure 3.1) is provided here.

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

Etranacogene Dezaparvovec Compared with Factor IX Prophylaxis in Adults with Hemophilia B

The initial success rate of etranacogene dezaparvovec appears excellent as long as the selected candidates do not have high antibody titers to the adenovirus vector used to deliver the therapy and that they receive the full dose. No patients meeting these criteria had to go back on factor prophylaxis during the first 18 months of therapy. Furthermore, bleeding rates (all types) were lower in years 4 and 5 in long term follow-up of the initial cohort of treated patients, but the number of patients was very low (n=5). It is not yet clear that the initial increase in factor IX levels will be maintained for decades, though the results are encouraging. Finally, the reduction in burden of therapy – no longer needing weekly or more frequent IX factor therapy – is a major benefit for patients. Because of the uncontrolled study design, small numbers of patients studied and relatively short follow-up, there is still considerable uncertainty about the long-term net benefits of etranacogene dezaparvovec compared with factor IX prophylaxis. In particular, there are uncertainties about the long-term impact of the therapy on liver function and the risk for hepatocellular carcinoma. However, the short-term results clearly favor etranacogene dezaparvovec and the harms seem relatively modest. Thus, we conclude that there is moderate certainty of a small or substantial health benefit with high certainty of at least a small net health benefit (B+) for etranacogene dezaparvovec compared with factor IX prophylaxis.

Valoctocogene Roxaparvovec Compared with Emicizumab in Adults with Hemophilia A

There is no direct evidence comparing valoctocogene roxaparvovec with emicizumab. Indirect evidence suggests that the short-term reduction in bleeding rates compared with factor prophylaxis with valoctocogene roxaparvovec is at least as great as that observed with emicizumab compared with factor prophylaxis. However, differences in the patient populations studied in the trials could be responsible for the observed benefits. Furthermore, there are clear initial adverse events with valoctocogene roxaparvovec (high risk of elevated liver enzymes requiring prolonged corticosteroid therapy). Because of the uncontrolled study design, small numbers of patients studied and relatively short follow-up, there is still considerable uncertainty about the long-term net benefits of etranacogene dezaparvovec compared with factor IX prophylaxis. In particular, there are uncertainties about the long-term impact of the therapy on liver function and the risk for hepatocellular carcinoma. Finally, as factor levels have been observed to decline over time, the benefits of valoctocogene roxaparvovec could be relatively short-lived. The lack of direct data comparing the two therapies, the small number of treated patients, and the modest long-term follow-up leave considerable uncertainty about the net health benefits. Thus, we conclude that there is low certainty about the net health benefit (I) for valoctocogene roxaparvovec compared with emicizumab.

Valoctocogene Roxaparvovec Compared with Factor VIII Prophylaxis in Adults with Hemophilia A

In ICER's 2020 review of valoctocogene roxaparvovec compared with factor VIII prophylaxis, we gave valoctocogene roxaparvovec a C++ rating. It is now clear that some patients get a significant benefit, while others get minimal to no benefit from valoctocogene roxaparvovec. Because of the uncontrolled study design, small numbers of patients studied and relatively short follow-up, there is still considerable uncertainty about the long-term net benefits of etranacogene dezaparvovec compared with factor IX prophylaxis. In particular, there are uncertainties about the long-term impact of the therapy on liver function and the risk for hepatocellular carcinoma. Finally, as factor levels have been observed to decline over time, the benefits of valoctocogene roxaparvovec could be relatively short-lived. Thus, we conclude that there is moderate certainty of a comparable, small, or substantial health benefit with high certainty of at least a comparable net health benefit (C++) for valoctocogene roxaparvovec compared with factor VIII prophylaxis.

Table 3.7. Evidence Ratings

Treatment	Comparator	Evidence Rating
Adults with Hemophilia B who Require Factor IX Prophylaxis		
Etranacogene Dezaparvovec	Factor Prophylaxis	B+
Adults with Hemophilia A who Require Factor VIII Prophylaxis		
Valoctocogene Roxaparvovec	Emicizumab	I
Valoctocogene Roxaparvovec	Factor Prophylaxis	C++

CTAF Votes

Table 3.8. CTAF Votes on Comparative Clinical Effectiveness Questions

Question	Yes	No
Patient Population for Question 1: Adults ≥ 18 years of age with hemophilia B without inhibitors who would be appropriate for routine prophylaxis with factor replacement**.** Is the evidence adequate to demonstrate that the net health benefit of etranocogene dezaparvovec is superior to that provided by prophylaxis with Factor IX?	10	2
Patient Population for Question 2-3: Adults ≥ 18 years of age with hemophilia A without inhibitors who would be appropriate for routine prophylaxis with factor replacement**.** Is the evidence adequate to demonstrate that the net health benefit of valoctocogene roxaparvovec is superior to that provided by prophylaxis with Factor VIII?	11	2
Is the evidence adequate to distinguish the net health benefit between valoctocogene roxaparvovec and prophylaxis emicizumab?	0	13

A majority of the panel voted that the evidence is adequate to demonstrate that the net health benefit of etranocogene dezaparvovec is superior to prophylaxis with Factor IX. While it was acknowledged that etranocogene desaparvovec does not show significant bleeding rate reductions, there is clinical benefit in being a less burdensome treatment. The panel expressed some hesitancy regarding etranocogene dezaparvovec's small, single-arm trial which was only tested in adults. The relatively modest harms of etranocogene dezaparvovec were also taken into account.

A majority of the panel voted that the evidence is adequate to demonstrate that the net health benefit of valoctocogene roxaparvovec is superior to prophylaxis with Factor VIII. Although valoctocogene roxaparvovec showed initial liver toxicity and increased rates of adverse events such as headaches, nausea, and fatigue, there is a clear benefit from bleed reductions. The severity of hemophilia A and therefore the potential for quality of life benefits for this population were also considered.

The panel voted unanimously that the evidence is not adequate to distinguish the net health benefit between valoctocogene roxaparvovec and prophylaxis emicizumab, acknowledging that there is no way to compare the patient populations of the two therapies. Due to differences in each study there were no meaningful recommendations found by the panel.

4. Long-Term Cost Effectiveness

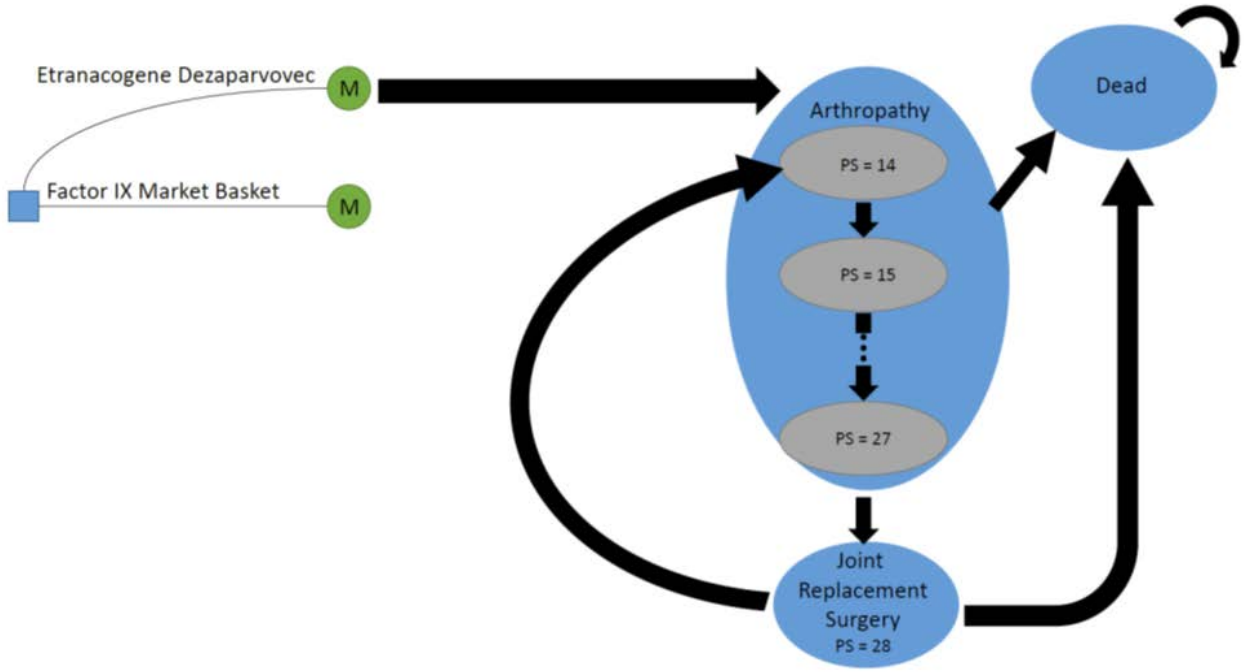
4.1. Methods Overview

We conducted an economic evaluation of etranacogene dezaparvovec for the treatment of hemophilia B patients without inhibitors eligible for prophylactic treatment and separately conducted an updated economic evaluation of valoctocogene roxaparvovec for the treatment of hemophilia A patients without inhibitors eligible for prophylactic treatment. A primary aim of this analysis was to evaluate the lifetime cost effectiveness of using etranacogene dezaparvovec, followed by initiation of prophylaxis with factor IX if needed, relative to prophylaxis with factor IX in patients with hemophilia B without inhibitors who are eligible for prophylactic treatment. A separate primary aim was to evaluate the lifetime cost effectiveness of using valoctocogene roxaparvovec, followed by initiation of prophylaxis with emicizumab as needed, relative to treatment with emicizumab in patients with hemophilia A without inhibitors who are eligible for prophylactic treatment.

There were two separate models each using the ICER ultra-rare disease framework with a health care sector perspective (i.e., focus on direct medical care costs only) over a lifetime time horizon. A modified societal perspective was also pursued as a scenario analysis, along with other scenarios described in the supplement. In addition, as both treatments in question are one time gene therapies, the analyses incorporated ICER's High-Impact Single and Short-Term Therapies (SST) framework including specific scenario analyses looking at optimistic and conservative long-term assumptions and at possible sharing of cost offsets between the manufacturer and society. Further, a specific outcomes-based warranty design suggested by BioMarin was incorporated into the traditional full cost-offset analysis projection in hemophilia A.

The first model compared etranacogene dezaparvovec to prophylactic treatment with factor IX. The second model, separately, compared valoctocogene roxaparvovec to prophylactic treatment with emicizumab. The models were developed in Microsoft Excel. Figure 4.1 below shows an overview of the model structure for hemophilia B. Hemophilia A has the same basic structure in terms of health states but of course had different treatments being compared. Each model projected costs, quality adjusted life years, equal value life years, life years, and total bleeds. Life years were equal in each arm in each model as there were no mortality impacts for the treatments and consequently evLYs were the same as QALYs. Each model separately projects the durability of treatment for gene therapy where when gene therapy is projected to lose efficacy there is initiation of prophylaxis with the other respective therapy arm.

Figure 4.1. Model Schematic



Following comments on the Draft Report, in this Report we have switched from using bleed rates for emicizumab in model 2 based on group B in the Haven Trial to group D in the Haven Trial. In Model 2 we include more details regarding the value-based agreement in the traditional full cost-offset analysis. We have included a disutility for prednisone use in the first cycle of model 1 and the first two cycles in model 2. We also include a scenario with relatively high AE related costs of $2200 in cycle one for model 1 and cycles 1 and 2 in model 2. In addition, we have changed the price for etranacogene dezaparvovec to $3.5 million as the list price. Finally, we identified a coding error that slightly changed the quality adjusted life year totals in the models, though did not impact the incremental results.

4.2. Key Model Assumptions and Inputs

Below is a list of key model choices common to both models:

- The structures of the models were based around the Pettersson score (PS). This allowed for longer model cycles, reducing computational complexity, while still accounting for bleeds each year as well as the development of arthropathy and the possibility of requiring surgery.
- Bleed rates determined transition rates across PS, and were key in projecting costs, and utilities in the model.

- Given treatment, mortality with hemophilia A or B is similar to the US average and there are no differential effects on mortality across the treatments.
- The models used 6-month cycles. This was the longest standard cycle that allowed for reasonable transition rates between PS counts each cycle, given the expected bleeding rates possible in the models.
- Costs and effects were discounted using a rate of 3%.
- Utilities derived from the published literature were weighted by the time spent in each health state.[33-37] The models included separate utilities for different types of bleed events, varying baseline utility by age and arthropathy, and utility associated with requiring surgery.
- The models included all direct treatment costs associated with each individual regimen, including drug acquisition costs and non-pharmacy costs (including all medical expenses associated with bleeds).
- All costs prior to 2021 were adjusted for inflation following methods outlined in the ICER reference case so that all cost inputs and outputs in the model reflect 2021 US dollars.

Key model choices specific to the hemophilia B model:

- Factor IX dosing and costs were based on available representative doses and proportions of use of those drugs provided by the manufacturers of etranacogene dezaparvovec.
  Bleed rates for etranacogene dezaparvovec were taken from the HOPE trial.[9] Available evidence on factor IX levels across time were used to consider the impact of declining efficacy across time for etranacogene dezaparvovec on bleed rates. Here projected factor activity levels below 5 IU/mL were assumed to lead to 5% of patients switching to factor IX and at levels below 1 IU/mL all patients switched to factor IX. When projected bleeds for etranacogene dezaparvovec are higher than the initial rates, the projected rates are used (see supplement for details).
- Bleed rates for factor IX were also based on baseline data from the HOPE trial.
- Etranacogene dezaparvovec was associated with a fixed utility gain of 0.03 per cycle as long as patients did not switch therapies based on data submitted by CSL Behring.
- Steroid use in the first cycle is modeled using costs of prednisone and a disutility of 0.03.[9]

Key model choices specific to the hemophilia A Model:

- Bleed rates across time for valoctocogene roxaparvovec in the hemophilia A model were derived from available data on factor levels seen in patients on that treatment in the GENEr8-1 trial adjusted to mimic 2% of patients per year for the first four years switching to prophylaxis and receiving payments from an outcomes-based four-year warranty intended to cover the cost of alternative prophylaxis treatment for the remainder of the warranty period. The manufacturer has provided, in confidence, more specific information to ICER on the payments anticipated for each year of the warranty, and potential triggers for the

warranty that include biomarker measurements, bleed rates, and decisions to return to prophylaxis. We also incorporate literature-based estimates of bleed rates across factor levels as efficacy declines. At projected factor activity levels below 5 IU/mL, 5% of valoctocogene roxaparvovec patients were assumed to switch to emicizumab prophylaxis. At projected factor activity levels below 1 IU/mL, all valoctocogene roxaparvovec patients were assumed to switch to emicizumab.

- Bleed rates were taken from the Haven 3 trial (group D) for emicizumab.[22]
- Proportions of all bleeds relative to treated bleeds in the HAVEN 3 trial along with proportions of all bleeds that are joint bleeds in the HAVEN 3 and POTTER trials were used to estimate different types of bleeds relative to treated bleeds for valoctocogene roxaparvovec.
- Factor VIII dosing and costs for treated bleeds were based on two representative treatments, Advate for standard half-life, and Eloctate for extended half-life, using doses of 50.4 IU/kg as was used in the previous ICER hemophilia A report.[31]
- Valoctocogene roxaparvovec was associated with a utility gain of 0.01 based on data submitted to ICER.[42]
- Steroid use is modeled for the first two cycles based on prednisone costs and a disutility of 0.03 [17]

The models included several assumptions that can be found in the supplement. See Table E2 for additional assumptions common to both models and specific assumptions for the hemophilia B model in Table E3 and specific assumptions for hemophilia A in Table E4 Additional details on the projections of bleed rates across time can also be found in the supplement.

Transition Probabilities

Transition probabilities between the PS-based health states in both models were based on expected annual joint bleed rates and a literature-based assumption that on average, 36.52 joint bleeds result in a one-point PS increase for patients under age 25 and 6.52 joint bleeds result in a one-point PS increase in patients aged 25 years or more.[43] Hence, the annual number of joint bleeds divided by 36.52 and subsequently by 6.52 as patients reach 25 years old can be thought of as an annual transition probability to the next higher PS. Annual bleed rates adjusted to 6-month time periods divided by 36.52 and then 6.52 corresponded to the transition rate using 6-month time cycles.

Following surgery, all patients (minus those expected to die from all causes) were assumed to return to the initial arthropathy health state with a PS of 14.

Utilities

Health state utilities in both models were derived from published literature sources and applied to the relevant health states. Baseline utility were taken from results of EQ-5D utilities based on responses from hemophilia patients broken out by age and degree of arthropathy, found in O'Hara et al (Table 4.4).[44] All of the disutilities associated with bleeds and with surgery used in the models were measured in patients with hemophilia A using the EQ-5D. We used the same health state utility values across treatments evaluated in both models. Utility in the surgery state were modelled using one month of having a time-tradeoff utility found in a general hip replacement patient group reported in the literature in 1993 (0.32) just prior to surgery, and 5 months with utility corresponding to a PS of 14-27 and the age of the patient getting surgery in the model

Drug Costs

Model 1

See Table E11 for details on dosing. Since etranacogene dezaparvovec was approved on November 22, the manufacturer announced a list price of $3,500,000. For the factor IX products we derived net prices from average sales prices (ASPs) to calculate treatment-related health care costs. As factor products are administered as an infusion at home, in an office or clinic under HCP supervision, use of ASP pricing was deemed most appropriate, which mirrors the approach taken in the 2020 Hemophilia A review. Per ICER's Reference Case, a 6% markup should be included in populations receiving Part B drugs; therefore, no adjustments were made to the ASP+6% prices reported in the July 2022 ASP pricing file. Proper HCPCS J codes for each agent were identified using billing, coding, and reimbursement guides as well as other resources.

Table 4.1. Drug Costs Model 1

Drug	Price per Dose	Discount Relative to Net	Net Price per Year*
Etranacogene Dezaparvovec	$3,500,000	N/A	N/A
Alprolix	$13,716	N/A	$744,303
Benefix	$5,307	N/A	$565,391
Idelvion	$13,419	N/A	$753,353
Rebinyn	$13,675	N/A	$713,552

*Costs of other drugs per dose are based on ASP per IU, 81.4kg weight and most often used IU/Kg dose. Costs per year are based on weighted average of usual doses with weights of 32.26%, 32.26%, 33.33%, and 2.15% for Alprolix, Benefix, Idelvion, and Rebinyn respectively.

Drug costs per bleed in the model were based on the most common dose and the market basket described above which amounted to $10,903.

Model 2

As valoctocogene roxaparvovec has not been approved, no WAC or net price estimates are available. We therefore conducted the full cost-offset analysis using a placeholder price of $2,500,000, based on statements from the manufacturer indicating consideration of prices of around $2 million to $3 million per treatment.[46] In the absence of data on usual discounts for gene therapy, we assumed no discounting and use this placeholder for the net price of this treatment. For the factor products in this analysis, we will derive net prices from average sales prices (ASP) to calculate treatment-related health care costs, as we do not have other data on net prices that included discounts/rebates for these agents. Per ICER's Reference Case, a 6% markup should be included in populations receiving Part B drugs; therefore, no adjustments will be made to the ASP+6% prices reported in the July 2022 ASP pricing file. As in model 1, proper HCPCS J codes for each agent will be identified using billing, coding, and reimbursement guides as well as other resources (see Table 4.2 below). In further accordance with ICER's reference we found a net price for emicizumab given its WAC rate minus a discount to align its cost to that reported by the U.S. Department of Veterans Affairs Federal Supply Schedule Service, as SSR Health discounts estimates of rebates or discounts were not available. As described above, warranty payments for treatment failure are included in the model and depend on the timing of the failure; based on information from the manufacturer, the model assumes a 2% failure rate per year for the first four years. Finally, we used costs for Prednisone 60mg for two months for the proportion of patients (85%) expected to experience elevations in alanine aminotransferase levels.

Table 4.2. Drug Costs Model 2

Drug	Price per Dose*	Discount from WAC*	Net Price per Year
Valoctocogene Roxaparvovec	$2,500,000	N/A	N/A
Emicizumab	$25,706	12%‡	$639,543†

*Price for emicizumab is based on a patient weighing 81.4; emicizumab price per dose corresponds to WAC.
† Assumes 3 mg/kg every 7 days for month 1; 3mg/kg every 14 days for month 2+
‡ Based on most recent U.S. Department of Veterans Affairs Federal Supply Schedule Service rate, as SSR rebate data did not exist for emicizumab

Drug costs per bleed, based on Advate and Eloctate were $7,253 for a patient weighing 81.4KG.

Non-Drug Costs

See details in the Supplement Tables E12, E13, and added details in the supplement on societal perspective costs.

4.3. Results

Full Cost-Offset Results

Model 1

Table 4.3 below shows the traditional full cost-offset results, including all standard of care cost offsets within the analysis, for model 1 using a price for etranacogene dezaparvovec of $3,500,000. Both treatment arms are projected to have extremely high lifetime costs, with etranacogene dezaparvovec having lower costs and slightly higher quality adjusted life years. Etranacogene dezaparvovec was also associated with lower bleeds. Life years are the same across treatments and consequently evLYs are the same as QALYs.

Table 4.3. Results for the Full Cost-Offset Analysis for Etranacogene Dezaparvovec Compared to Factor IX

Treatment	Drug Cost	Total Cost	Bleeds	QALYs	Life Years	evLYs
Etranacogene Dezaparvovec	$8,500,000*	$9,454,000	182	20.03	27.13	20.03
Factor IX	$14,029,000	$15,797,000	247	19.39	27.13	19.39

evLYG: equal value life years gained, QALY: quality-adjusted life year

Table 4.4 below shows the incremental results. Etranacogene dezaparvovec and factor IX had identical QALYs and evLYs, and etranacogene dezaparvovec was projected to be a dominant treatment with lower total costs (including costs of factor IX use when patients switch) and higher QALYs.

Table 4.4. Incremental Cost-Effectiveness Ratios for the Full Cost-Offset Analysis for Etranacogene Dezaparvovec Compared to Factor IX

Treatment	Comparator	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained	Cost per bleed averted
Etranacogene Dezaparvovec	Factor IX	Dominant	Undefined	Dominant	Dominant

evLYG: equal value life years gained, QALY: quality-adjusted life year
These are based on a cost of etranacogene dezaparvovec of $3,500,000.

Model 2

Table 4.5 below shows the traditional full cost-offset results, including all standard of care cost offsets within the analysis, for model 2 using a placeholder price of $2,500,000 for valoctocogene roxaparvovec. Both treatment arms are projected to have extremely high lifetime costs with valoctocogene roxaparvovec having lower costs and slightly higher quality adjusted life years. Valoctocogene roxaparvovec was also associated with slightly lower bleeds. Life years are the same across treatments and consequently evLYs are the same as QALYs.

Table 4.5. Results for the Full Cost-Offset Analysis for Valoctocogene Roxaparvovec Compared to Emicizumab

Treatment	Drug Cost	Total Cost	Bleeds	QALYs	Life Years	evLYs
Valoctocogene Roxaparvovec	$13,635,000*	$14,076,000	171	19.64	27.13	19.64
Emicizumab	$17,492,000	$18,084,000	177	19.54	27.13	19.54

evLYG: equal value life years gained, QALY: quality-adjusted life year
*These are based on a placeholder cost for valoctocogene roxaparvovec of $2,500,000.

Table 4.6 below shows the incremental results. Valoctocogene roxaparvovec and emicizumab had identical life years and evLYs, and valoctocogene roxaparvovec was projected to be a dominant treatment with lower costs, very slightly lower bleeds and higher QALYs.

Table 4.6. Incremental Cost-Effectiveness Ratios for the Full Cost-Offset Analysis for Valoctocogene Roxaparvovec Compared to Emicizumab

Treatment	Comparator	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained	Cost per Bleed Averted
Valoctocogene Roxaparvovec	Emicizumab	Dominant	Undefined	Dominant	Dominant

These are based on a placeholder cost of valoctocogene roxaparvovec of $2,500,000.

Sensitivity Analyses

Model 1

See Supplement for details. For all ranges of all the inputs the incremental costs of etranacogene dezaparvovec were substantially lower and incremental QALYs were higher. In addition, in all simulations in the probabilistic sensitivity analyses etranacogene dezaparvovec was cost effective at all willingness to pay thresholds.

Model 2

See Supplement for details. In all sensitivity analyses incremental costs were lower and QALYs higher for valoctocogene roxaparvovec. In the probabilistic sensitivity analyses valoctocogene roxaparvovec was cost effective in all simulations at all willingness to pay thresholds.

Scenario Analyses

As discussed in greater detail in Section 6, ICER has concluded that in situations where a large percentage of the traditional Health Benefit Price Benchmark (HBPB) comes from cost offsets of therapies that, themselves, have prices that are not believed to be aligned with benefits to patients (e.g., factor therapies for hemophilia A and B), ICER will present ranges from shared savings calculations as the most policy-relevant HBPBs. In such situations and when cost offsets are substantially above $300,000 annually, ICER will generally focus on the $150,000 annual cap on offsets shared savings analysis as being the most policy relevant. Existing therapies that cost far in excess of $150,000 per year can be assumed to have prices that are not aligned with benefits and therefore require adjustments to traditional cost-effectiveness analyses. The $150,000 annual cap on cost offsets adjusts the costs within standard of care such that an intervention's ability to change standard of care will result in a maximum of $150,000 in cost savings per year.

See the Supplement tables in Section E5 for details on all scenario analyses. For the $150,000 annual cap on offsets analysis, using either the list price (if available) or placeholder price mentioned above, in model 1, etranacogene dezaparvovec was found to have an incremental cost-effectiveness ratio of $997,000 per QALY. Similarly, for the $150,000 annual cap on offsets analysis, in model 2, valoctocogene roxaparvovec was found to have a cost-effectiveness of $5.3 million per QALY.

Threshold Analyses

Table 4.7 below displays the threshold prices at various threshold levels for the traditional full cost-offset analysis, as well as for the analysis with capped savings of $150,000 per year, shared savings, and one with no savings to the health system from the gene therapies. As the incremental health gains between etranacogene dezaparvovec and factor IX were small, the difference in price across the threshold levels is relatively small.

Table 4.7. QALY-Based Threshold Analysis Results for Etranacogene Dezaparvovec

	Unit Price to Achieve $50,000 per QALY Gained	Unit Price to Achieve $100,000 per QALY Gained	Unit Price to Achieve $150,000 per QALY Gained	Unit Price to Achieve $200,000 per QALY Gained
$150,000 Cap Scenario	$2,894,000	$2,926,000	$2,958,000	$2,990,000
Shared Savings (50:50)	$5,066,000	$5,098,000	$5,130,000	$5,162,000
No Savings*	$258,000	$290,000	$322,000	$354,000
Full Cost-Offset Analysis	$9,875,000	$9,907,000	$9,939,000	$9,971,000

QALY: quality-adjusted life year

*During the first model cycle, no savings are attributed to etranacogene dezaparvovec due to the acquisition costs of the intervention being accounted for in the first cycle; therefore, the "no savings" threshold prices were slightly higher when compared to valuing any health gains at a cost per health gain threshold

Table 4.8 shows the threshold prices for valoctocogene roxaparvovec. In the $150,000 capped annual savings scenario the threshold price is lower than the placeholder price. Again, because the health gains were small between valoctocogene roxaparvovec and emicizumab, the difference in price across threshold levels is relatively small.

Table 4.8. QALY-Based Threshold Analysis Results for Valoctocogene Roxaparvovec

	Unit Price to Achieve $50,000 per QALY Gained	Unit Price to Achieve $100,000 per QALY Gained	Unit Price to Achieve $150,000 per QALY Gained	Unit Price to Achieve $200,000 per QALY Gained
$150,000 Cap Scenario	$1,951,000	$1,956,000	$1,961,000	$1,966,000
Shared Savings (50:50)	$3,456,000	$3,461,000	$3,467,000	$3,472,000
No Savings*	$324,000	$329,000	$335,000	$340,000
Full Cost-Offset Analysis	$6,701,000	$6,706,000	$6,711,000	$6,717,000

QALY: quality-adjusted life year

*During the first model cycle, no savings are attributed to valoctocogene roxaparvovec due to the acquisition costs of the intervention being accounted for in the first cycle; therefore, the "no savings" threshold prices were slightly higher when compared to valuing any health gains at a cost per health gain threshold

Durability Thresholds

We examined durability thresholds to see how long each gene therapy, followed by initiation of prophylaxis treatment, would have to maintain efficacy to become cost effective relative to the comparator, assuming the traditional full cost-offset analysis. We did this specifically by having 100 percent of patients switch to the comparator each cycle one by one to see the impact on the results. We found that etranacogene dezaparvovec transitions from not being cost effective at $150,000 per QALY to being a dominant treatment at 7.5 years at a price of $3,500,000. Valoctocogene roxaparvovec transitions from not cost effective to dominant in year 4 (cycle 8) at a placeholder price of $2,500,000.

Model Validation

Model validation details can be found in the Supplement.

Uncertainty and Controversies

- There was limited data on the efficacy of the gene therapies and limited mechanisms for projecting bleeds across time
- There is limited data to project the durability of the gene therapies
- There is insufficient data in either patient population to evaluate the potential future impact of not being eligible for future gene therapies should the initial gene therapy fail
- The relationship between joint bleeds and surgery is imperfect and the model assumes one joint surgery at a time likely undercounting surgeries in all of the model arms
- Utility scores for bleeds come from patients with inhibitors
- The utility scores in the models come from patients with underlying health states

- The bleed data for both arms in model 1 come from trial data which may differ from rates in actual practice
- The bleed comparisons in model 2 are based on indirect comparisons across patient populations and settings
- Finally, we have a placeholder price for valoctocogene roxaparvovec

4.4 Summary and Comment

The gene therapies have large cost savings associated with them with very large lifetime costs associated with both the treatments and comparators in both models. In addition, the gene therapies are associated with slightly higher QALYs and lower bleeds. Overall, the full cost-offset results in both models were robust to a wide range of sensitivity analyses as well as scenario analyses varying inputs and assumptions in the model. In the capped cost savings scenario for gene therapy of $150,000 per year, using the respective prices, the gene therapies were not cost effective even at higher thresholds, illustrating that the cost-saving results were sensitive to the cost of the respective comparators being well above $150,000 per year.

5. Contextual Considerations and Potential Other Benefits

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

Table 5.1. Contextual Considerations

Contextual Consideration	Relevant Information
Acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability	With current prophylactic treatments, the short-term risk of death or progression to permanent disability is relatively small.
Magnitude of the lifetime impact on individual patients of the condition being treated	Most patients have a normal life expectancy, but joint bleeding causes life-long disability associated with joint damage.

Table 5.2. Potential Other Benefits or Disadvantages

Potential Other Benefit or Disadvantage	Relevant Information
Patients' ability to achieve major life goals related to education, work, or family life	If gene therapy is successful and generates several years of high factor levels, it could allow a patient to choose a period in life where they desire freedom from therapies for hemophilia. This could allow choices about education, career activities, travel, or sports that might otherwise never be possible. The potentially time limited impact of the therapy may apply more to current gene therapy for hemophilia A than for therapy for hemophilia B as current data suggest that etranacogene dezaparvovec may be more durable.
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life	Hemophilia imposes significant burdens on caregivers. Often caregivers work part time or are unemployed due to the time needed to perform their care duties supporting the patient with hemophilia.
Patients' ability to manage and sustain treatment given the complexity of regimen	Gene therapy is a major step forward for patients who need to inject factor prophylaxis intravenously. Adherence with therapy is no longer an issue, although there are significant burdens in the first year of treatment (laboratory testing, barrier contraception, avoiding nephrotoxins, etc.). The reduction in complexity is particularly true for people with hemophilia B, but a bit less for people with hemophilia A who have the option of emicizumab delivered subcutaneously.
Society's goal of reducing health inequities	Unlikely to reduce health inequities.

CTAF VOTES

At the public meeting, the CTAF deliberated and voted on the relevance of specific potential other benefits and contextual considerations on judgments of value for the interventions under review. The results of the voting are shown below. Further details on the intent of these votes to help provide a comprehensive view on long-term value for money are provided in the ICER Value Assessment Framework [HYPERLINK].

When making judgments of overall long-term value for money, what is the relative priority that should be given to *any* effective treatment for hemophilia A, on the basis of the following contextual considerations:

Contextual Consideration	Very Low Priority	Low priority	Average priority	High priority	Very high priority
Acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability	3	3	6	0	0
Magnitude of the lifetime impact on individual patients of the condition being treated	0	0	1	8	4

Half of the panel voted that based on the acuity of need for treatment of individual patients with hemophilia A, average priority should be given to any treatment. There were some votes for low and very low priority, with panel members citing that there is generally no acute short-term risk of death for a chronic illness such as hemophilia A. A majority of the panel agreed on the high priority for any effective treatment regarding the magnitude of the lifetime impact of hemophilia A.

When making judgments of overall long-term value for money, what is the relative priority that should be given to *any* effective treatment for hemophilia B, on the basis of the following contextual considerations:

Contextual Consideration	Very Low Priority	Low priority	Average priority	High priority	Very high priority
Acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability	2	2	6	1	1
Magnitude of the lifetime impact on individual patients of the condition being treated	0	0	0	6	7

Half of the panel voted that based on the acuity of need for treatment of individual patients with hemophilia B, average priority should be given to any treatment. However, there were some votes for high and very high priority, acknowledging the slightly different context for hemophilia B in which prophylaxis is the only current therapy. All of the panelist voted for high or very high priority regarding the magnitude of the lifetime impact of hemophilia B.

What are the relative effects of etranacogene dezaparvovec versus prophylaxis with Factor IX on the following outcomes that inform judgment of the overall long-term value for money of etranacogene dezaparvovec?

Potential Other Benefit or Disadvantage	Major Negative Effect	Minor Negative Effect	No Difference	Minor Positive Effect	Major Positive Effect
Patients' ability to achieve major life goals related to education, work, or family life	0	0	1	2	10
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life	0	0	0	11	2
Patients' ability to manage and sustain treatment given the complexity of regimen	0	0	0	4	9

A majority of the panel voted that etranacogene dezaparvovec would have a major positive effect on patients' ability to achieve major life goals related to education, work, or family life. A majority voted for a minor positive effect on a caregivers' ability to achieve such goals, acknowledging gene therapies do not currently apply to children who may be most likely to use a caregiver. Despite the high amount of monitoring required in the first year of treatment, a majority of the panel voted that etranacogene dezaparvovec would have a major positive effect on patients' ability to manage and sustain treatment given the complexity of the regime.

What are the relative effects of valoctocogene roxaparvovec versus prophylaxis with emicizumab on the following outcomes that inform judgment of the overall long-term value for money of valoctocogene roxaparvovec?

Potential Other Benefit or Disadvantage	Major Negative Effect	Minor Negative Effect	No Difference	Minor Positive Effect	Major Positive Effect
Patients' ability to achieve major life goals related to education, work, or family life	0	0	3	9	1
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life	0	0	9	3	1
Patients' ability to manage and sustain treatment given the complexity of regimen	0	0	1	9	2

A majority of the panel voted that valoctocogene roxaparvovec would have a minor positive effect on patients' ability to achieve major life goals related to education, work, or family life, whereas a majority of the panel voted for no difference on careivers' quality of life, again citing that this is currently a treatment for adults. Given that this treatment eliminates many burdens associated with subcutaneous therapies, a majority of the panel voted that the treatment would have a minor positive effect on patients' ability to manage and sustain treatment given the complexity of the regimen.

6. Health Benefit Price Benchmarks

Health Benefit Price Benchmarks (HBPBs) for the annual cost of treatment with the intervention(s) are presented in Table 6.1 below. The HBPB for a drug is defined as the price range that would achieve incremental cost-effectiveness ratios between $100,000 and $150,000 per QALY or per evLY gained.

ICER's High-Impact Single and Short-Term Therapies (SST) framework includes analyses that look at shared savings of cost offsets from a new therapy. ICER has concluded that in a situation where a large percentage of the traditional HBPB comes from cost offsets of therapies that, themselves, have prices that are not believed to be aligned with benefits to patients, ICER will present ranges from one of the SST shared savings calculations as the most policy-relevant HBPBs. When annual cost offsets are below $300,000 annually, ICER will generally focus on the SST 50:50 shared savings results; when they are substantially above $300,000 annually, ICER will generally focus on the SST $150,000 annual cap on offsets results. Existing therapies that cost far in excess of $150,000 per year can be assumed to have prices that are not aligned with benefits.

For this report, we calculate that more than 99% of the traditional HBPB results for both valoctocogene roxaparvovec and etranacogene dezaparvovec come from offsetting the price of prophylaxis with existing agents that cost far in excess of $300,000 per year. See Section E6 in the Supplement. As such, the HBPB ranges presented are calculated using the $150,000 annual cap on offsets from the SST framework.

For valoctocogene roxaparvovec, the HBPB is $1.96 million to $1.96 million. For etranacogene dezaparvovec, the HBPB is $2.93 million to $2.96 million.

CTAF Votes

Table 6.1. CTAF Votes on Long-Term Value for Money at Current Prices

Question	Low long-term value for money at current pricing	Intermediate long-term value for money at current pricing	High long-term value for money at current pricing
Given the available evidence on comparative effectiveness, incremental cost effectiveness, and potential other benefits or disadvantages, what is the long-term value for money of treatment at current pricing with etranacogene dezaparvovec versus prophylaxis with Factor IX?	5	7	1

The majority of the panel voted that etranacogene dezaparvovec at its current price provides low to intermediate long-term value for money. The panel had been asked to consider a price of $4,000,000 based on input from the manufacturer, however the subsequent price chosen by the manufacturer was $3,500,000. This reflected the uncertainties regarding limited data to project the durability of the gene therapies. There were also five votes for low long-term value for money, with panel members concluding that too much of the value reflected offsetting costs of overpriced Factor IX prophylaxis and their caution of continuing treatment inflation. One panel member voted for high long-term value for money, noting that at a price of $4,000,000, etranacogene dezaparvovec would be cost saving.

7. Potential Budget Impact

7.1 Overview of Key Assumptions

We used results from the cost-effectiveness model to estimate the potential total budgetary impact of each new drug for the severe hemophilia A and B adult male populations without inhibitors. For each intervention in the cost-effectiveness analyses, we use either the list price (if available) or the placeholder price and the three threshold prices (at $50,000, $100,000, and $150,000 per QALY) in our estimates of budget impact. The aim of the potential budgetary impact analyses is to document the percentage of patients who could be treated at select prices without crossing a potential budget impact threshold that is aligned with overall growth in the US economy. For 2022-2023, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to be approximately $777 million per year for new drugs.

Potential budget impact is defined as the total differential cost of using each new therapy rather than relevant existing for the treated populations, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. In our model analysis plan, we outlined that we planned to use results from the same models employed in the cost-effectiveness analyses to estimate total potential budget impact for both etranacogene dezaparvovec (potential budget impact analysis [PBIA] 1) and valoctocogene roxaparvovec (PBIA 2).

For PBIA 1, using Centers for Disease Control (CDC) data and other sources, we estimated that approximately 860 adult severe hemophilia B patients without inhibitors would be eligible for treatment with etranacogene dezaparvovec. This equates to approximately 172 patients being treated per year over 5 years when assuming 20% of all eligible patients are treated each year. In PBIA 1, we calculate the budget impact associated with displacing use of existing factor IX therapies, comprising a basket mirroring that used in the cost-effectiveness analyses, with etranacogene dezaparvovec.

A formal budget impact analysis ultimately was not conducted for the severe hemophilia A population (PBIA 2) as valoctocogene roxaparvovec was associated with cost savings over a five-year time horizon when compared to emicizumab therapy.

For each analysis, either the list price (if available) or the placeholder price was considered as well as the $150,000 annual savings cap threshold prices over the range of $50,000 to $150,000/QALY, as these are the threshold prices used to generate the health benefit price benchmark (HBPB) range.

7.1 Results

For PBIA 1, all patients could be treated with etranacogene dezaparvovec at its price without crossing the annual budget impact threshold. As the HBPB range for etranacogene dezaparvovec is lower than its price, this estimate held true for HBPB price estimates as well. At its price, etranacogene dezaparvovec accounted for 49% ($377 million) of the annual budget impact threshold of $777 million. These findings were driven by the high costs of factor therapy at baseline (i.e., "current" budget impact analysis scenario).

Access and Affordability Alert

As no known publicly available price exists for valoctocogene roxaparvovec, we are unable to fully estimate its budgetary impact and are therefore not issuing an access and affordability alert for this therapy. Further, we are not issuing an access and affordability alert for etranacogene dezaparvovec as its maximum budgetary impact over 5 years at its acquisition cost of $3.5 million is not anticipated to exceed ICER's potential budget impact threshold of $777 million per new therapy per year for the US population. Cost-effectiveness analyses suggest that etranacogene dezaparvovec is cost saving over longer (e.g., lifetime) time horizons.

8. Policy Recommendations

Following its deliberation on the evidence, the CTAF engaged in a moderated discussion with a policy roundtable about how best to apply the evidence on the use of etranacogene dezaparvovec and valoctocogene roxaparvovec. The policy roundtable members included two patient advocates, two clinical experts, two payers, and two representatives from the drug makers. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. The top-line policy implications are presented below, and additional information can be found here.

All Stakeholders

The value of high-impact single and short-term therapies should not be determined exclusively by estimates of long-term cost offsets, particularly when the existing standard of care is acknowledged to be priced significantly higher than reasonable cost-effective levels.

New single and short-term therapies offer the potential for significant health gains for patients, including in some cases the possibility of a lifelong cure from a chronic illness. The value of such treatments is substantial, in part because they may obviate the need for years of expensive chronic care. But that value must be tempered by several considerations. First, at launch only relatively short-term data are available, and therefore there is relatively high uncertainty regarding the durability of the beneficial treatment effect, while unknown long-term risks are also possible. And second, when the costs of the current standard of care exceed levels that reflect the opportunity cost for new treatments in the health system, simply aggregating those costs over the lifetime of patients and assigning all potential cost offsets to the "value" of the new one-time therapy, magnifies the existing distortion of value and pricing in the US health care system, denying the chance for the health system to recoup some of the cost savings so that innovation can be kept more affordable for all patients. Assigning the full cost offset to the single price of a gene therapy also creates a distortion in the incentives for innovation, skewing them strongly away from addressing conditions that are either fatal in the short term, such as genetic diseases of newborns, or that have few added health care costs, such as blindness. As one of the CTAF voting members said at the public meeting "*Today we had to consider a standard of care that is priced at levels that are not consistent with our society's views. Although the easiest thing to do is to endorse anything cheaper than that, I think in doing so we will encourage unsustainable pricing that will limit the care we can provide to all patients.*"

Given these contextual factors, all stakeholders and policymakers should avoid using traditional cost-effectiveness analysis alone as a guide to considerations of fair pricing. Capping credit for cost offsets in some way should be explored further as an alternative approach to calculating ranges of fair pricing. This report provided several different scenarios of ways to "share savings" from a

potential cure. These options and other ways to address these broader questions should be considered today to prepare for "fair pricing" of the cures of tomorrow.

Payers

Recommendation 1

Payers should work with manufacturers to develop and implement outcomes-based agreements to address the uncertainty and the high cost of gene therapies for hemophilia.

Although there are important practical challenges, the best approach available for US payers to address the uncertainty and high cost of gene therapies is to work with manufacturers to develop and implement outcomes-based agreements. An important principle in this effort should be to start with a fair price. Although manufacturers hold substantial leverage in price negotiation over promising gene therapies, they should not set prices beyond reasonable levels linked to cost-effectiveness analyses simply to cover the costs of paying back higher rebates should treatments not meet expected targets for safety or durability of benefits.

Payers should ensure that they have addressed key details when operationalizing any outcomes-based agreement for gene therapies for hemophilia. The outcomes used to define treatment failure need to be clear and should include both low factor levels and clinical bleeding. Failing by either criterion should trigger the rebate or warranty provision. Payers may also want to negotiate to have the manufacturer at risk for full coverage of any factor therapy used during the warranty period. In addition, just as patients with their providers decide whether and when to choose gene therapy, they should be empowered to decide when gene therapy has failed, and the patient should have no barriers in receiving coverage for resuming factor prophylaxis. It should be noted that patients treated with gene therapy will still require on-demand factor therapy, which should be available when needed for situations such as trauma and surgery in addition to spontaneous bleeding episodes.

Because small employers are at risk for severe financial toxicity if one or two of their covered employees/families require a gene therapy, payers should consider offering programs that protect plan sponsors (and their employees) by mechanisms such as carved out PMPM coverage plans for cell and gene therapies.

Manufacturers

Recommendation 1

The pricing in the US of all factor replacement therapies and of emicizumab represents a failure of competition and is far too high, even considering the substantial benefits of prophylaxis for patients; this pricing structure creates financial toxicity for patients and their families, financial

toxicity for health systems, and builds a platform for pricing for potential cures that will only exacerbate these problems. Concrete steps by the federal government are likely needed to achieve prices more reasonably aligned with patient benefit.

Factor prices have not come down despite competition among multiple products and the loss of 60% of overall market share of factor VIII therapy to emicizumab. There are several different options for addressing the lack of market forces to restrain pricing. The US could follow the European model of having the government ask companies to compete for a sole tender and pick a single or a more limited set of factor products, using a competitive bidding process to keep prices closer to a reasonable alignment with overall patient benefit. Alternatively, in the multi-payer commercial insurance market, PBMs and health plans could seek to use the same approach to seek deeper rebates using narrower formularies, but even large PBMs are likely to lack the market power to restrict access in this way. Perhaps the best way to maintain broad access to multiple agents within a more affordable framework would be for the US to negotiate or set price ceilings for all factor agents based on value assessment. This approach would retain substantial incentives for future innovation, particularly for one-time curative therapies, but would ensure that the prices paid for hemophilia treatment accomplishes more good than the harm that arises from increasing health insurance costs for vulnerable individuals.

Patient Organizations

Recommendation 1

Patient organizations are to be praised for their proactive development of objective descriptions of the risks and benefits of gene therapies to support shared decision-making for every patient.

The hemophilia patient community is particularly sophisticated in their understanding of the uncertainties and potential harms of novel therapies given the devastating experience of the community with hepatis C and HIV infections. Patient groups should continue to collaborate to develop education materials that educate patients about the potential risks and benefits of gene therapies and continue their work with other stakeholders to develop and disseminate evidence-based, balanced materials that are accessible to all patients, including those with low health literacy. It is essential that patients receive a consistent set of information about the potential benefits and harms from advocacy organizations, their health care providers and from the manufacturers to ensure true shared decision-making when considering an irreversible treatment like gene therapy.

Recommendation 2

Patient organizations have a powerful voice and should apply it to create significant pressure for fair pricing and appropriate insurance coverage across all sectors of the health system.

We applaud the National Hemophilia Foundation, Hemophilia Foundation of America, and the Coalition for Hemophilia B for their joint public comments on our draft report highlighting that 'the current cost of hemophilia treatment is "financially toxic" for PwH, their families, and the health care systems on which they depend. The finding that gene therapy is cost effective does not mean it is affordable, that it will be accessible within the marketplace post- approval, or that it is an optimal treatment for every eligible patient. We remain concerned that high target prices will impede access to these potentially transformative therapies.'

Patient groups should also take responsibility to publicly promote both improved access and fair pricing of new therapies for Hemophilia A and B. Patient groups should additionally follow-up such statements with organized campaigns to advocate for fair pricing, for example, by encouraging patients and families to write to Congress or launch public relation campaigns with such messaging.

Patient groups should also continue their efforts to ensure that patients are aware of programs to assist them and their families with insurance coverage and care. For example, patients over the age of 21 in California may be eligible for coverage and other assistance under the Genetically Handicapped Persons Program (GHPP). Living with Hemophilia is challenging for all, but especially those with socioeconomic barriers, and to improve health equity within the hemophilia community special efforts should be made to reach out to individuals and families who may not be as "plugged in" to current options for best care.

Researchers/Regulators

Recommendation 1

Because of the novelty of gene therapy and the uncertainties about the long-term benefits and harms of these interventions, all patients treated with gene therapy should be enrolled in long term follow-up registries.

Currently we have only two to three years of follow-up for patients enrolled in the phase 3 clinical trials of these two gene therapies for hemophilia. We need much longer follow-up to better understand the benefits and potential harms of these therapies. Both cancer incidence and liver disease as well as factor levels and bleeding rates merit particular focus in these studies. Given the rarity of hemophilia and expected incidence of potential harms, all gene therapy recipients should be enrolled in a longitudinal global research / surveillance registry. Regulators should require manufacturers to underwrite the cost of these registries.

Recommendation 2

Because of the novelty of gene therapy, the complexity of its delivery, and ongoing safety concerns, the FDA should put in place a Risk Evaluation and Mitigation Strategy (REMS) as requested by the National Hemophilia Foundation on July 1, 2022 for both etranadez and valrox.

Specifically, the NHF requested that the FDA should include the inclusion and exclusion criteria from the phase 3 trials in the labeling of the therapies. In addition, there should be a certification process for each center that administers these gene therapies and specific training for physicians and other healthcare providers delivering gene therapy and following patients after they have received gene therapy. The intent of the proposed REMS is to ensure safe and appropriate use of the gene therapy.

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Supplemental Materials

A. Background: Supplemental Information

A1. Definitions

Severe Hemophilia: Factor VIII or IX levels less than 1 percent.[47]

Moderately Severe Hemophilia: Factor VIII or IX levels equal to or greater than 1 percent and less than 2 percent.[29]

Normal Factor Activity: Factor VIII or IX levels ranging from 50 to 100 percent.[47]

Target Joint: 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.[6]

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.[48]

Haemophilia Quality of Life Questionnaire for Adults (Haem-A-Qol): A hemophilia-specific, 46-item evaluating ten domains of helath-related quality of life (HRQoL) in patients ages 17 and older. Scores range from of 0 (best HRQoL) to 100 (worst HRQoL).[49]

Hemophilia-Specific Quality Of Life Questionnaire For Adults (Haemo-Qol-A): A hemophilia-specific, 41-item instrument evaluating six domains of HRQoL in adult patients: physical functioning, role functioning, worry, bleeding consequences, emotional impact, and treatment concerns. Scores range from of 0 (worst HRQoL) to 100 (best HRQoL).[50]

A2. Potential Cost-Saving Measures in Hemophilia

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see https://icer.org/our-approach/methods-process/value-assessment-framework/). These services are ones that would not be directly affected by therapies for hemophilia (e.g., reduction in disability), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of hemophilia beyond the potential offsets that arise from a new intervention. During stakeholder engagement and public comment periods, ICER encouraged all stakeholders to suggest services

(including treatments and mechanisms of care) currently used for patients with either hemophilia A or hemophilia B that could be reduced, eliminated, or made more efficient. No suggestions were received.

B. Patient Perspectives: Supplemental Information

B1. Methods

To inform our undersanding of the patient perspective, we had two focus groups with patients and we spoke with representatives from the National Hemophila Foundation, the Hemophilia Federation of America, the Coalition for Hemophilia B, the European Haemophilia Consortium, and Mark Skinner. We also reviewed and summarized the patient perspective from prior ICER reports on hemophilia A.

C. Clinical Guidelines

National Hemophilia Foundation, Medical and Scientific Advisory Council (MASAC) Recommendations, MASAC Document 272 - MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Other Bleeding Disorders, March 2020[51]

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

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

Similarly, the MASAC guidelines state that recombinant factor IX products are the recommended treatment of choice for patients with hemophilia B.

Genetic therapy is not addressed as the guideline only covers licensed therapies.

World Federation of Hemophilia: Guidelines for the Management of Hemophilia 2020, 3rd edition[52]

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

WFH recommends early initiation of prophylaxis (before age 3 and before onset of joint disease) with clotting factor for pediatric patients with severe hemophilia. Dosing and dosing interval for prophylaxis with clotting factor (either standard or extended half-life) should be sufficient to prevent spontaneous and breakthrough bleeding, and hemarthrosis. In the event of breakthrough

bleeds even while on a prophylactic regimen, the WFH recommends escalation of prophylactic dose and orthopedic interventions, as necessary.

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

British Society for Haematology, Guidelines on the Use of Prophylactic Factor Replacement for Children and Adults with Haemophilia A and B, May 2020[53]

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

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

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

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

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

D. Comparative Clinical Effectiveness: Supplemental Information

D1. Detailed Methods

PICOTS

Population

The population of focus for this review was adults ≥ 18 years of age with hemophilia B or A without inhibitors who would be appropriate for routine prophylaxis with factor replacement.

Interventions

The interventions of interest for this review are listed below:

- Etranacogene dezaparvovec for hemophilia B
- Valoctocogene roxaparvovec for hemophilia A

Comparators

We compared etranacogene dezaparvovec to factor IX prophylaxis. We compared valoctocogene roxaparvovec to factor VIII prophylaxis and emicizumab specifically.

Outcomes

Patients and patient groups directed us to review the core outcome set established through coreHEM, an international multi-stakeholder project that convened 49 experts (patients, clinicians, researchers, drug developers, methodologists, regulators, health technology assessors and payers) to identify a core set of outcomes for hemophilia gene therapy trials.[54] Specifically, the coreHEM project identified six core outcomes as crucial for evaluating the effectiveness of gene therapy: frequency of bleeds, factor activity level, duration of expression, chronic pain, mental health status, and utilization of the healthcare system (direct costs).[54] The coreHEM outcomes have been integrated in our outcome list below.

For this review, we will look for evidence on the following outcomes of interest:

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

  Other Outcomes:

    - Factor level (factor activity level)
    - Duration of expression of the clotting factor gene
    - Utilization of healthcare system
    - Adverse events including:
        - Immune response to factor (Inhibitor development)
        - Immune response to gene therapy

Of note, factor level is an extremely important surrogate/intermediate outcome when thinking about gene therapy, but it is not, in itself, a patient-important outcome. Patients with identical factor levels can have important differences in their experience of disease. In addition, different assays for factor levels can give markedly different results. However, over higher ranges the factor level is an excellent surrogate, and a therapy that provides normal, sustained factor levels would be expected to achieve normal hemostasis in patients with hemophilia.

We sought out evidence on additional patient-reported outcomes, such as employment, disability status, social engagement, overall well-being, mobility (activity), anxiety, and depression, as available, as well as outcomes for family and caregivers.

Timing

Evidence on intervention effectiveness was derived from studies of any duration, as long as they meet the study design criteria set forth above and measure the outcomes of interest.

Settings

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

Study Design

Randomized controlled trials, non-randomized controlled trials, comparative observational studies, and single-arm (non-comparative) studies with any sample size were included.

Table D1. PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review.	
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	

	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	
Study characteristics	17	Cite each included study and present its characteristics.	
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	
Results of syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.	
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	
	23b	Discuss any limitations of the evidence included in the review.	
	23c	Discuss any limitations of the review processes used.	
	23d	Discuss implications of the results for practice, policy, and future research.	

OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
Availability of data, code, and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

From: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *PLoS Med.* 2021;18(3):e1003583.

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on new therapies for hemophilia B and A followed established best research methods. We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[57] The PRISMA guidelines include a checklist of 27 items.

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

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see https://icer.org/policy-on-inclusion-of-grey-literature-in-evidence-reviews/. Where feasible and deemed necessary, we also accepted data submitted by manufacturers "in-confidence," in accordance with ICER's published guidelines on acceptance and use of such data (https://icer.org/guidelines-on-icers-acceptance-and-use-of-in-confidence-data-from-manufacturers-of-pharmaceuticals-devices-and-other-health-interventions/).

Table D2. Etranacogene Dezaparvovec for Hemophilia B: EMBASE

	Search Term
1	'hemophilia B'/exp
2	('hemophilia b' OR 'haemophilia b' OR 'blood clotting factor 9 deficiency' OR 'blood clotting factor ix deficiency' OR 'christmas disease' OR 'congenital blood clotting factor 9 deficiency' OR 'congenital blood clotting factor ix deficiency' OR 'congenital clotting factor 9 deficiency' OR 'mckusick 30690'):ti,ab
3	#1 OR #2
4	('Etranacogene dezaparvovec' OR 'Etranacogene dezaparvovec' OR 'AMT061' OR 'AMT 061' OR 'AMT-061' OR 'AMT060' OR 'AMT 060' OR 'AMT-060' OR 'AAV5-HFIX' OR 'recombinant adeno-associated viral vector containing a codon-optimized Padua derivative of human coagulation factor IX cDNA' OR 'AAV5-Padua' OR 'AAV5-hFIXco-Padua'):ti,ab
5	#3 AND #4
6	#5 NOT ('addresses' OR 'autobiography' OR 'bibliography' OR 'biography' 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')/it

7	#6 NOT ([animal cell]/lim OR [animal experiment]/lim OR [animal model]/lim OR [animal tissue]/lim OR (mouse OR murine OR mice):ti)
8	#7 AND [English]/lim
9	#8 NOT [medline]/lim

Search last ran on October 03, 2022

Table D3. Etranacogene dezaparvovec for Hemophilia B: 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, Cochrane Central Registers of Controlled Trials and Systematic Reviews

#	Search Term
1	exp hemophilia b/
2	("Hemophilia B" or "Bs, Hemophilia" or "Hemophilia Bs" or "Deficiency, Factor IX" or "Deficiencies, Factor IX" or "Factor IX Deficiencies" or "Factor IX Deficiency" or "Hemophilia B Leyden" or "Hemophilia B(M)" or "Hemophilia Bs (M)" or "Plasma Thromboplastin Component Deficiency" or "F9 Deficiency" or "Deficiencies, F9" or "Deficiency, F9" or "F9 Deficiencies" or "Christmas Disease" or "Disease, Christmas" or "Haemophilia B" or "Haemophilia Bs").ti,ab.
3	1 or 2
4	("Etranacogene dezaparvovec" or "Etranacogene dezaparvovec" or "AMT061" or "AMT 061" or "AMT-061" or "AMT060" or "AMT 060" or "AMT-060" or "AAV5-HFIX" or "recombinant adeno-associated viral vector containing a codon-optimized Padua derivative of human coagulation factor IX cDNA" or "AAV5-Padua" or "AAV5-hFIXco-Padua").ti,ab.
5	3 and 4
6	5 not ("address" or "autobiography" or "bibliography" or "biography" or "case reports" or "comment" or "congress" or "consensus development conference" or "corrected and republished article" or "duplicate publication" or "editorial" or "guideline" or "interview" or "lecture" or "legal case" or "legislation" or "letter" or "news" or "newspaper article" or "patient education handout" or "periodical index" or "personal narrative" or "portrait" or "practice guideline" or "published erratum" or "review" or "video-audio media").pt.
7	6 not ((animals not (animals and humans)).sh. or (mice or mouse or murine or animal or animals or sheep or canine or macaques or monkey or rat).ti.)
8	limit 7 to English language

Search last ran on October 03, 2022

Table D4. Valoctocogene roxaparvovec and Emicizumab for Hemophilia A: EMBASE

	Search Term
1	'hemophilia A'/exp
2	('hemophilia a' OR 'haemophilia a' OR 'haemophilia vera' OR 'hemophilia plasma' OR 'hemophilia vera' OR 'hemophylia type a' OR 'mckusick 30670' OR 'true haemophilia' OR 'true hemophilia' OR 'ahf deficiency' OR 'ahg deficiency' OR 'antihaemophilic factor deficiency, congenital' OR 'antihemophilic factor deficiency, congenital' OR 'blood clotting factor 8 deficiency' OR 'blood clotting factor viii deficiency' OR 'classic haemophilia' OR 'classic hemophilia' OR 'clotting factor 8 deficiency, congenital' OR 'congenital antihaemophilic factor deficiency' OR 'congenital antihaemophilic globulin deficiency' OR 'congenital antihemophilic factor deficiency' OR 'congenital antihemophilic globulin deficiency' OR 'congenital blood clotting factor 8 deficiency' OR 'congenital blood clotting factor viii deficiency' OR 'congenital clotting factor 8 deficiency' OR 'factor viii deficiency'):ti,ab
3	#1 OR #2
4	('Valoctocogene Roxaparvovec' OR 'Valoctocogene roxaparvovec' OR 'Roctavian' OR 'BMN 270' OR 'BMN270' OR 'BMN-270' OR 'Factor VIII gene therapy' OR 'AAV5-hfVIII-SQ' OR 'AAV5hfVIII' OR 'AAV5 hfVIII'):ti,ab

5	('emicizumab' OR 'Hemilibra' OR 'hBS910' OR 'ACE910' OR 'ACE 910' OR 'ACE-910' OR 'RG6013' OR 'RG 6013' OR 'RG-6013' OR 'RO 5534262' OR 'RO5534262' OR 'RO-5534262' OR 'ch 5534262; ch5534262; emicizumab kxwh; emicizumab-kxwh'):ti,ab
6	#3 AND (#4 OR #5)
7	#6 NOT ('addresses' OR 'autobiography' OR 'bibliography' OR 'biography' 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')/it
8	#7 NOT ([animal cell]/lim OR [animal experiment]/lim OR [animal model]/lim OR [animal tissue]/lim OR (mouse OR murine OR mice):ti)
9	#8 AND [English]/lim
10	#9 NOT [medline]/lim
11	#10 AND [01/01/2020]/sd

Search last ran on October 03, 2022

Table D5. Valoctocogene roxaparvovec and Emicizumab for Hemophilia A: 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, Cochrane Central Registers of Controlled Trials and Systematic Reviews

	Search Term
1	exp hemophilia a/
2	("Hemophilia A" or "Hemophilia As" or "Hemophilia, Classic" or "Hemophilia" or "Hemophilia A, Congenital" or "Congenital Hemophilia A" or "Congenital Hemophilia As" or "Hemophilia As, Congenital" or "Classic Hemophilia" or "Classic Hemophilias" or "Hemophilias, Classic" or "Haemophilia" or "Autosomal Hemophilia A" or "As, Autosomal Hemophilia" or "Autosomal Hemophilia As" or "Hemophilia A, Autosomal" or "Hemophilia As, Autosomal" or "Factor VIII Deficiency" or "Factor 8 Deficiency, Congenital" or "Factor VIII Deficiency, Congenital" or "Deficiency, Factor VIII").ti,ab
3	1 or 2
4	("Valoctocogene Roxaparvovec" or " Valoctocogene roxaparvovec" or " Roctavian" or " BMN 270" or " BMN270" or " BMN-270" or " Factor VIII gene therapy" or " AAV5-hFVIII-SQ" or " AAV5 hFVIII" or " AAV5hFVIII").ti,ab.
5	("emicizumab" or " Hemilibra" or " hBS910" or " ACE910" or " ACE 910" or " ACE-910" or " RG6013" or " RG 6013" or " RG-6013" or " RO 5534262" or " RO5534262" or " RO-5534262" or " ch 5534262" or " ch5534262" or " emicizumab kxwh" or " emicizumab-kxwh").ti,ab
6	3 and (4 or 5)
7	6 not ("address" or "autobiography" or "bibliography" or "biography" or "case reports" or "comment" or "congress" or "consensus development conference" or "corrected and republished article" or "duplicate publication" or "editorial" or "guideline" or "interview" or "lecture" or "legal case" or "legislation" or "letter" or "news" or "newspaper article" or "patient education handout" or "periodical index" or "personal narrative" or "portrait" or "practice guideline" or "published erratum" or "review" or "video-audio media").pt.
8	7 not ((animals not (animals and humans)).sh. or (mice or mouse or murine or animal or animals or sheep or canine or macaques or monkey or rat).ti.)
9	limit 8 to English language
10	limit 9 to ed=20200101-20221003

Search last ran on October 03, 2022

Figure D1. PRISMA Flow Chart: Results of Literature Search for Etranacogene Dezaparvovec for Hemophilia B

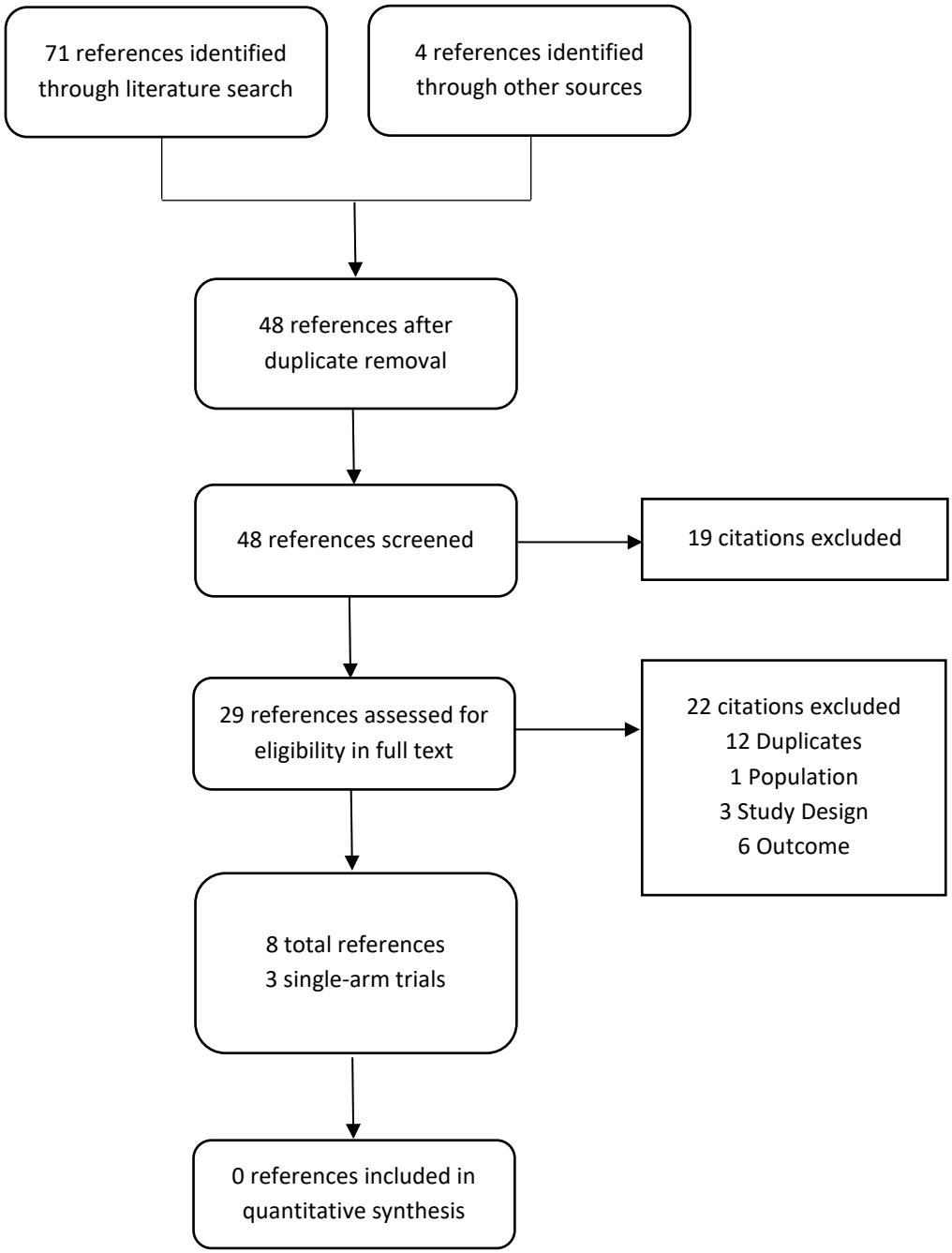
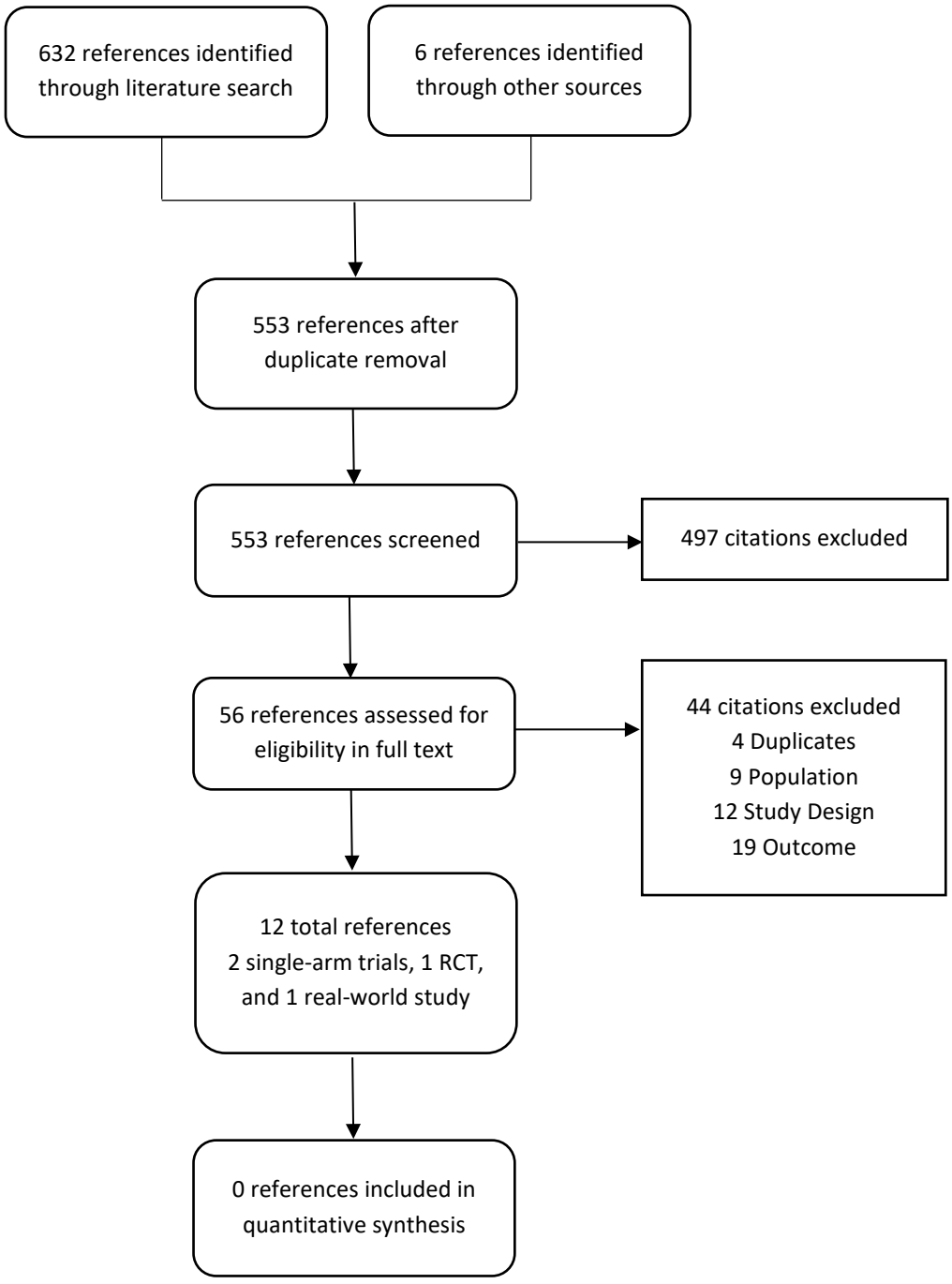


Figure D2. PRISMA Flow Chart: Results of Literature Search for Valoctocogene Roxaparvovec and Emicizumab for Hemophilia A



Study Selection

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. Two investigators reviewed full papers and provided justification for exclusion of each excluded study.

We also included FDA documents related to etranacogene dezaparvovec and valoctocogene roxaparvovec. These included the manufacturer's submission to the agency, internal FDA review documents, and the transcript of Advisory Committee deliberations and discussions.

Data Extraction and Quality Assessment

Data were extracted into Excel (Microsoft Corporation). Two reviewers abstracted data on study design, baseline characteristics of the study population, efficacy outcomes, safety, and health-related quality of life from included references. Data were validated by a second reviewer.

Because included studies were non-randomized and did not have a placebo or control arm, we did not assign any quality ratings. The limitations, uncertainties, and gaps in evidence of these trials are discussed in the Uncertainty and Controversies section.

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus.

Assessment of 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 etranacogene dezaparvovec and valoctocogene roxaparvovec using clinicaltrials.gov. Search terms included "etranacogene dezaparvovec," "valoctocogene roxaparvovec", "hemophilia B", and "hemophilia A". We selected studies which would have met our inclusion criteria and for which no findings have been published. We provided qualitative analysis of the objectives and methods of these studies to ascertain whether there may be a biased representation of study results in the published literature.

Data Synthesis and Statistical Analyses

Data on relevant outcomes were summarized in evidence tables (see Supplement D2) and synthesized qualitatively in the body of the review. Based on the differences in study population, study design, and outcomes assessed we did not conduct quantitative syntheses between the gene therapies and factor prophylaxis.

D2. Evidence Tables

Table D6. Study Design: Etranacogene Dezaparvovec, Valoctocogene Roxaparvovec, and Emicizumab Studies

Trial	Study Design	Inclusion/Exclusion Criteria	Key Outcomes [Timepoint]
Etranacogene dezaparvovec for Hemophilia B			
HOPE-B Trial of AMT-061 in Severe or Moderately Severe Hemophilia B Patients	**PHASE 3** Open label, multi-center, single-dose, single-arm **Dose**: $2x10^{13}$ gc/kg N = 54	**Inclusions** - Males ages ≥18 years - Congenital hemophilia B (severe/moderately severe) currently on factor IX prophylaxis - >150 previous exposure days of treatment with factor IX protein **Exclusions** - History of or current positivity to factor IX inhibitors - Select screening laboratory value >2 times upper limit of normal - Uncontrolled HIV, active hepatitis B or C virus - Previous gene therapy/experimental agent 60 days prior to trial	**Primary** - Annualized bleeding rate [52 weeks] **Secondary** - Factor IX activity [18 months] - Factor IX consumption - Adverse events - Health-related quality of life
AMT-061-01 Dose-Confirmation Trial of AAV5-hFIXco-Padua	**PHASE 2b** Open label, multi-center, single-dose, single-arm **Dose**: $2x10^{13}$ gc/kg N = 3	**Inclusions** - Males ages ≥18 years - Congenital hemophilia B (severe/moderately severe) - >20 previous exposure days of treatment with FIX protein **Exclusions** - History or current positivity of FIX inhibitors at screening - Select screening laboratory values > 2 times upper normal limit - Positive uncontrolled HIV at screening - Active Hepatitis B or C infection at screening or history of Hepatitis B or C exposure, currently controlled by antiviral therapy	**Primary** - Factor IX activity levels [6 weeks] **Secondary** - Adverse events [5 years] - Annualized bleeding rate [52 weeks] - Use of factor IX replacement therapy [52 weeks]
Valoctocogene roxaparvovec for Hemophilia A			
GENEr8-1 Single-Arm Study To Evaluate The Efficacy and Safety of Valoctocogene	**PHASE 3** Open label, multi-center, single-arm, single-dose **Dose:** $6x10^{13}$ vg/kg	**Inclusions** - Males ages ≥18 years - Hemophilia A and residual FVIII levels ≤ 1 IU/dL as evidenced by medical history - Prophylactic FVIII replacement therapy for ≥12 months	**Primary** - Factor VIII activity [52 weeks] **Secondary** - Utilization of exogenous Factor VIII replacement therapy [52 weeks]

Roxaparvovec in Hemophilia A Patients (BMN 270-301)	N = 134	prior to study entry - Treated/exposed to FVIII concentrates or cryoprecipitate for a minimum of 150 exposure days. - No history of a detectable FVIII inhibitor or current inhibitors ≥ 0.6 Bethesda Units/mL **Exclusions** - Detectable pre-existing antibodies to the AAV5 capsid. - Active HIV, chronic or active hepatitis B, active hepatitis C - Active malignancy, except non-melanoma skin cancer, or history of hepatic malignancy.	- Annualized number of bleeding episodes requiring Factor VIII replacement treatment [52 weeks]
BMN 270-201 Gene Therapy Study in Severe Haemophilia A Patients (270-201)	**PHASE 1/2** Open label, single-arm, dose-escalation **Dose**: $6x10^{13}$ vg/kg and $4x10^{13}$ vg/kg N = 15*	**Inclusions** - Males ages ≥18 years - Established severe Hemophilia A (FVIII level ≤1 IU/dL) - Treated/exposed to FVIII concentrates or cryoprecipitate for a minimum of 150 exposure days - ≥12 bleeding episodes for patients on on-demand FVIII replacement therapy over the previous 12 months - No history of inhibitor, or >0.6 Bethesda Units **Exclusions** - Detectable pre-existing immunity to the AAV5 capsid as measured by AAV5 transduction inhibition or AAV5 total antibodies - Immunosuppressive disorder or active chronic infection including hepatis B, hepatitis C, HIV - Significant liver dysfunction as defined by abnormal elevation of liver function tests	**Primary** - Treatment-related adverse events [85 Months] - Dose of AAV5-hFVIII-SQ required to achieve Factor VIII ≥5% of normal activity (>5 IU/dL) [85 months] **Secondary** - Immune response [85 Months] - Frequency of FVIII replacement therapy [85 months] - Number of bleeding episodes requiring treatment [85 months]
Emicizumab for Hemophilia A			
HAVEN 3 A Clinical Trial to Evaluate Prophylactic Emicizumab Versus no Prophylaxis in Hemophilia A Participants Without Inhibitors (HAVEN 3)	**PHASE 3** Randomized, open-label, multi-center, multi-dose **Dose**: 1.5 mg/kg/week and 3 mg/kg/2 weeks N = 152	**Inclusions** - Ages ≥12 years - Severe congenital hemophilia A - Documented use of FVIII treatment and number of bleeding episodes in last 6 months **Exclusions** - Inherited or acquired bleeding disorder other than hemophilia A - Previous or current treatment for thromboembolic disease or signs of thromboembolic disease	**Primary** - Annualized bleeding rate for treated bleeds [24 weeks] **Secondary** - Annualized bleeding rate for other types of bleeds - Health-related quality of life

		- Known HIV infection with cluster of differentiation 4 count <200 cells per microliter within 24 weeks prior to screening. - Use of systemic immunomodulators at enrollment or planned use during the study	

Information from clinicaltrials.gov

*Only including data on 7 patients in the $6x10^{13}$ vg/kg cohort

gc: genome copies, HIV: human immunodeficiency virus, IU/dL: international units per deciliter, kg: kilograms, mg: milligram, N: total number, vg: vector genomes

Table D7. Etranacogene Dezaparvovec Baseline Characteristics

		HOPE-B Phase 3	**AMT-061-01** Phase 2b
Study Arm & Dose		Overall ($2x10^{13}$ gc/kg)	Overall ($2x10^{13}$ gc/kg)
N		54	3
Age, years	**Mean (SD)**	41.5 (15.8)	46.7 (3.5)
	Median (range)	37.0 (19, 75)	47 (43, 50)
Sex, n (%)	**Male**	54 (100)	3 (100)
Race, n (%)	**Asian**	2 (3.7)	0
	Black or African American	1 (1.9)	2 (66.7)
	White	40 (74.1)	1 (33.3)
	Other	6 (11.1)	0
Severity, n (%)	**Moderately Severe**	10 (18.5)	1 (33.3)
	Severe	44 (81.5)	2 (66.7)
Presence of Target Joints, n (%)	**Yes**	2 (3.7)	NR
	No	52 (96.3)†	NR
Participants on Factor Prophylaxis, n (%)	**Extended half-life**	31 (57.4)	3 (100)
	Standard half-life	23 (42.6)	NR
	Prophylactic	54 (100)	NR
	On-demand/Episodic	4 (7.4)	NR
Pre-study Annualized Rate of Treated Bleeds, mean		3.98	NR
Zero Bleeds in Year Prior to Screening, n (%)		10 (18.5)	0
Characteristics not reported: Native Hawaiian/Pacific Islander race, pre-study annualized factor use, annualized factor infusions, and median annualized rate of treated bleeds			

gc/kg: genome copies per kilogram, SD: standard deviation, n: number, N: total number, NR: not reported

Table D8. Durability of Factory Activity: Etranacogene Dezaparvovec

		Baseline	Month 6	Month 12	Month 18	Month 24	Month 30	Month 36
One-Stage Assay Factor Activity IU/dL								
HOPE B Phase 3	**N evaluated**	54	51	50	50	**AIC**	NYR	NYR
	Mean (SD)	1.2*	39.0 (18.7)	41.5 (21.7)	36.9 (21.4)	**AIC**		
	% Change	reference	96.8*	97.1*	96.8*	NR		
	Mean Change (SD); p-value	reference	37.77 (18.78); <0.0001	40.3*	35.72 (21.46); <0.0001	NR		
	Median (range)	NR	NR (8.2-97.1)	NR (5.9-113.0)	NR (4.5-122.9)	NR		
AMT-061-01 Phase 2b	**N evaluated**	1	NR	3	NR	3	3	2
	Mean (SD)	5.10		40.8 (9.45)		44.2 (7.66)	50.0 (11.4)	36.9 (6.51)
	% Change	reference		87*		88*	90*	86*
	Mean Change	reference		35.67*		39.1*	44.9	31.8*
	Median (range)	NR		40.8 (31.3, 50.2)		44.7 (36.3, 51.6)	54.4 (37.1, 58.6)	NR (32.3, 41.5)
Not reported: Factor activity via chromogenic substrate assay (CSA), durability of the annualized bleeding rate of treated bleeds								

* ICER calculation

95%CI: 95 percent confidence-interval, AIC: academic-in-confidence, IU/dL: international units per deciliter, IQR: interquartile range, N: total number, NR: not reported, NYR: not yet reported, SD: standard deviation

Table D9. Factor IX Use and Discontinuation: Etranacogene dezaparvovec

			Factor use, IU/kg/year	Factor infusions/year
HOPE-B Phase 3 N = 54	**6-month Lead-In**	**Mean (SD)**	257,339	NR
	Etranacogene dezaparvovec 7-18 months post-dose	**Mean (SD)**	8,487*	
		% Reduction	97	
		Mean Change (SD); p-value	-248,825 (21,102); <0.0001	
		Discontinuation of factor prophylaxis, n (%)	52 (96.3)	
AMT-061-01 Phase 2b N = 3	**6-month Lead-In**	**Mean (SD)**	NR	NR
	Etranacogene dezaparvovec 7-18 months post-dose	**Mean (SD)**	1220.4 (1078.8)	0.67 (NR)
		% Reduction	NR	NR
		Mean Change	NR	NR

			Factor use, IU/kg/year	Factor infusions/year
		Discontinuation of factor prophylaxis, n (%)	3 (100)	

* Months 13-18
IU/kg: international units/kilogram, mo: months, N: total number, NR: not reported, SD: standard deviation

Table D10. Annualized Bleeding Rates: Etranacogene dezaparvovec HOPE-B Phase 3

	All Bleeds	Treated Bleeds	Joint Bleeds	Treated Joint Bleeds	Spontaneous Bleeds	Treated Spontaneous Bleeds
6-month Lead-In (N = 54)						
Adjusted ABR (95%CI)	4.19 (3.22, 5.45)	3.65 (2.82, 4.74)	2.35 (1.74, 3.16)	2.13 (1.58, 2.88)	1.52 (1.01, 2.30)	1.34 (0.87, 2.06)
N with 0 bleeds (%)	14 (25.9)	17 (31.5)	22 (40.7)	23 (42.6)	30 (55.6)	32 (59.3)
Etranacogene dezaparvovec Month 7-18 post-dose (N = 54)						
Adjusted ABR (95%CI)	1.51 (0.81, 2.82)	0.84 (0.41, 1.73)	0.51 (0.23, 1.12)	0.44 (0.19, 1.00)	0.44 (0.17, 1.12)	0.45 (0.15, 1.39)
% Reduction	64	77	78	80	71	66
Rate Ratio (95%CI); p-value	0.36 (0.20, 0.64); 0.0002*	0.23 (0.12, 0.46); <0.0001*	0.22 (0.10, 0.46); <0.0001*	0.20 (0.09, 0.45); <0.0001*	0.29 (0.12, 0.71); 0.0034*	0.34 (0.11, 1.00); 0.0254
N with 0 bleeds (%)	34 (63.0)	39 (72.2)	43 (79.6)	45 (83.3)	45 (83.3)	48 (88.9)
Not reported: Median annualized bleeding rate, treated target-joint bleeds, treated traumatic bleeds						

* Statistically significant
95%CI: 95 percent confidence interval, ABR: annualized bleeding rate, N: total number

Table D11. Bleeds: Etranacogene Dezaparvovec Phase 2b[13]Table D11. Bleeds: Etranacogene Dezaparvovec Phase 2b[13]

	Pre-treatment	2.5 Years Post-Treatment
N	3	3
All Bleeds, mean*	3.33	0.67
Spontaneous Bleeds, mean*	0	0.33
Traumatic bleeds, mean*	0	0.33

* ICER calculated

Table D12. Safety: Etranacogene Dezaparvovec

		HOPE-B Phase 3	AMT-061-01 Phase 2b
N		54	3
Follow-up		52 weeks	2.5 years
Adverse Events, n (%)	**Overall**	53 (98)	3 (100)
	Serious	NR	1 (33.3)
Treatment-Related Adverse Events, n (%)	**Overall**	39 (72.2)	1 (33.3)
	Serious	0	0
Mortality, n (%)	**Overall**	1 (1.9)	0
	Adverse event-related	0	0
Adverse Events of Special Interest			
Headache, n (%)	**Overall**	NR	2 (66.7)
	Treatment-related	8 (14.8)	NR
Arthralgia, n (%)	**Overall**	NR	NR
	Treatment-related	3 (5.6)	NR
Nausea, n (%)	**Overall**	NR	NR
	Treatment-related	4 (7.4)	NR
Fatigue, n (%)	**Overall**	NR	NR
	Treatment-related	4 (7.4)	NR
Infusion-Related Reaction, n (%)	**Overall**	NR	NR
	Treatment-related	7 (13.0)	NR
Influenza, n (%)	**Overall**	NR	NR
	Treatment-related	7 (13.0)	NR
Upper Respiratory Tract Infection, n (%)	**Overall**	NR	1 (33.3)
	Treatment-related	NR	NR
Nasopharyngitis, n (%)	**Overall**	NR	NR
	Treatment-related	NR	NR
Alanine Aminotransferase Increase, n (%)	**Overall**	NR	1 (33.3)
	Serious	NR	0
	Treatment-related	9 (16.7)	NR
Aspartate Aminotransferase Increase, n (%)	**Overall**	NR	1 (33.3)
	Treatment-related	5 (9.3)	NR
Glucocorticoid Use	**n (%)**	9 (16.7)	0
	Mean Dose, mg	NR	N/A

		HOPE-B Phase 3	AMT-061-01 Phase 2b
	Mean Duration, days (range)	79	N/A
Factor Inhibitor Development, n (%)		NR	0
Malignancies, n (%)		1 (1.9)	NR
Outcomes not reported: Grade 3/4 adverse events, glucocorticoid-related adverse events, thrombotic events			

ALT: alanine aminotransferase, AST: aspartate aminotransferase, mg: milligram, N/A: not applicable, n: number, N: total number, NR: not reported

Table D13. Health-Related Quality of Life: Etranacogene Dezaparvovec HOPE-B Phase 3

	6 month Lead-in, Mean (SE)	Etranacogene dezaparvovec 52-weeks post-dose, Mean (SE)	LS Mean Difference (SE); p-value	% Change
Haemophilia Quality of Life Questionnaire for Adults (Haem-A-Qol)†				
Total	25.56 (2.072)	20.06 (2.054)	-5.50 (0.972); <0.0001*	21.50
Feelings	20.61 (2.838)	11.19 (2.790)	-9.42 (1.938); <0.0001*	45.70
Treatment	25.24 (1.857)	10.36 (1.804)	-14.88 (1.789); <0.0001*	59.00
Work/School	17.34 (2.555)	12.35 (2.534)	-4.99 (1.825); 0.0036*	28.78
Future	30.94 (2.753)	25.92 (2.712)	-5.02 (1.736); 0.0023*	16.22
Physical Health	31.16 (3.744)	26.95 (3.698)	-4.21 (2.181); 0.0278	13.5
EuroQol-5 Dimension (EQ-5D)				
EQ-5D-5L‡	0.7943 (0.02919)	0.8253 (0.02877)	0.031 (0.019); 0.0530	NR
EQ-5D-VAS§	80.9 (2.20)	81.0 (2.15)	0.1 (1.84); 0.4753	NR
Health-related quality of life not reported for AMT-061-01 (Phase 2b)				

* Statistically significant
† Scores range from 0 to 100; lower scores indicate better quality of life
‡ Scores range from 0 to 1; higher scores indicate better quality of life
§ Scores range from 0 to 100; higher scores indicate better quality of life
LS: least-squares, NR: not reported, SE: standard error

Table D14. Baseline Characteristics: Valoctocogene Roxaparvovec and Emicizumab

		Valoctocogene roxaparvovec					Emicizumab	
		GENEr8-1 Phase 3				BMN 270-201 Phase 1/2	HAVEN 3 Phase 3	
Study Arm & Dose		mITT (>2 years)	Rollover	mITT	ITT	6x10^13 vg/kg	Factor VIII (NIS)	Group D
N		17	112	132	134	7	49	63
Age, years	Mean (SD)	29.5 (6.0)	31.8 (10.6)	31.4 (10.1)	31.7 (10.3)	30.4 (5.8)	NR	36.4 (14.4)
	Median (range)	29.0 (19, 43)	30.0 (19, 70)	30.0 (18, 70)	30.0 (18, 70)	30 (23, 42)	35.0 (13-68)	36.0 (13, 68)
Sex, n (%)	Male	17 (100)	112 (100)	132 (100)	134 (100)	7 (100)	49 (100)	63 (100)
Race, n (%)	Asian	1 (6)	17 (15.2)	19 (14.4)	19 (14.2)	1 (14.3)	9 (18.4)	12 (19.0)
	Black or African American	1 (6)	14 (12.5)	15 (11.4)	15 (11.2)	0	1 (2.0)	1 (1.6)
	Native Hawaiian/ Pacific Islander	0	1 (0.9)	1 (0.8)	1 (0.7)	0	NR	0
	White	14 (82)	78 (69.6)	94 (71.2)	96 (71.6)	6 (85.7)	37 (75.5)	47 (74.6)
Severity, n (%)	Moderately Severe	0	0	0	0	0	0	0
	Severe	17 (100)	112 (100)	132 (100)	134 (100)	7 (100)	49 (100)	63 (100)
Presence of Target Joints, n (%)	Yes	NR	NR	37 (28.0)	NR	NR	NR	26 (41.3)
	No	NR	NR	95 (72.0)	NR	NR	NR	37 (58.7)
Participants on Factor Prophylaxis, n (%)	Extended half-life	7 (41)	28 (25.0)	36 (27.3)	37 (27.6)	NR	NR	10 (15.9)
	Standard half-life	10 (59)	69 (61.6)	81 (61.4)	83 (61.9)	NR	NR	130 (86.1)
	Prophylactic	NR	NR	NR	NR	6 (85.7)	NR	63 (100)
	On-demand/Episodic	NR	NR	NR	NR	1 (14.3)	NR	0
Prestudy Annualized Factor Use - IU/kg	Mean (SD)	4830.0 (1578.1)	3961.2 (1751.5)	4111.3 (1747.8)	4113.5 (1739.0)	NR	NR	NR
	Median (range)	4635.0 (2550.9, 7885.0)	3754.4 (1296.4, 11251.1)	3860.3 (1296.4, 11251.1)	3860.3 (1296.4, 11251.1)	NR	NR	NR
Prestudy Annualized Factor Infusions	Mean (SD)	152.9 (86.6)	135.9 (52.0)	138.1 (57.2)	137.5 (57.0)	120.1 (45.9)	NR	NR
	Median (range)	119.7 (49.3, 358.7)	128.6 (39.5, 363.8)	125.1 (39.5, 363.8)	121.1 (39.5, 363.8)	121.4 (27.4, 158.5)	NR	NR

		Valoctocogene roxaparvovec					Emicizumab	
		GENEr8-1 Phase 3				BMN 270-201 Phase 1/2	HAVEN 3 Phase 3	
Study Arm & Dose		mITT (>2 years)	Rollover	mITT	ITT	6x10^13 vg/kg	Factor VIII (NIS)	Group D
Prestudy Annualized Rate of Treated Bleeds	**Mean (SD)**	9.5 (22.5)	4.8 (6.5)	5.4 (10.0)	5.4 (10.0)	17.6 (14.7)	3.08†	NR
	Median (range)	0.9 (0, 91.5)	2.8 (0, 33.1)	2.0 (0, 91.5)	2.3 (0, 91.5)	24.0 (0, 40.0)	NR	NR
Characteristics not reported: Participants with zero bleeds in the year prior to screening								

ITT: intention-to-treat, IU/kg: international units, kg: kilogram, mITT: modified intention-to-treat, n: number, N: total number, NIS: non-interventional study, NR: not reported, SD: standard deviation, vg: vector genome

Table D15. Durability of Factory Activity: Valoctocogene Roxaparvovec

		Baseline	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
One-Stage Assay Factor Activity - IU/dL								
GENEr8-1 Phase 3 mITT	**N evaluated**	NR	132‡	NYR	NYR	NYR	NYR	NYR
	Mean		*64.3*					
	Median		*40.3*					
GENEr8-1 Phase 3 mITT >2 years follow-up	**N evaluated**	NR	17‡	17‡	NYR	NYR	NYR	NYR
	Mean		*65.1*	*38.6*				
	Median		*38.6*	*24.8*				
BMN 270-201 Phase 1/2	**N evaluated**	NR	NR	NR	NR	NR	NR	NR
	Mean		104	59	52	35.4	NR	17
	Median		NR	NR	NR	NR	NR	12.8
Chromogenic Substrate Assay Factor Activity - IU/dL								
GENEr8-1 Phase 3 mITT	**N evaluated**	132‡	132‡	132‡	NYR	NYR	NYR	NYR
	Mean (SD)	1†	42.9 (45.5)	*23.2 (NR)*				
	% Change	reference	98*	96*				
	Mean Change (95%CI); p-value	reference	41.9 (34.1, 49.7); 0.001	22.2*				
	Median (IQR)	NR	23.9 (11.9-62.3)	NR				
GENEr8-1 Phase 3 mITT >2 years follow-up	**N evaluated**	17‡	17‡	17‡	17‡	NYR	NYR	NYR
	Mean (SD)	1†	42.2 (50.9)	24.4 (29.2)	*16.9 (NR)*			
	% Change	reference	98*	96*	NR			
	Mean Change (95%CI); p-value	reference	41.2*	23.4*	NR			
	Median (IQR)	NR	23.9 (11.2-55.0)	14.7 (6.4-28.6)	NR			
BMN 270-201 Phase 1/2	**N evaluated**	NR	7	7	7	6	7	NR
	Mean		64.3	36.4	32.7	24.2	11.6	9.8
	Median (IQR)		60.3 (46.6, 88.4)	26.2 (24.1, 51.7)	19.9 (100.8, 45.9)	16.4 (9.2, 29.5)	8.2 (1.6, 18.6)	5.6 (NR)

Italicized data are digitized and should be interpreted with caution.
* ICER calculation

	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6

† Baseline factor activity imputed as 1 IU/dL

‡ Missing data imputed LOCF

95%CI: 95 percent confidence interval, IQR: interquartile range, IU/dL: international units per deciliter, mITT: modified intention-to-treat, N: total number, NR: not reported, NYR: not yet reported, SD; standard deviation

Table D16. Factor IX Use and Discontinuation: Valoctocogene Roxaparvovec & Emicizumab

		Factor use, IU/kg/year	Factor infusions/year
Valoctocogene roxaparvovec GENEr8-1 Phase 3	**6-month Lead-In (N = 112)**		
	Mean (SD)	3961.2 (NR)	135.9 (NR)
	Median (range)	3754.4 (NR)	128.6 (NR)
	Valoctocogene roxaparvovec 2 years post-dose (N = 112)		
	Mean (SD)	70 (NR)	2.6 (NR)
	% Reduction	98.2	98
	Mean Change (SD); p-value	-3891 (-4221, -3562); 0.0001*	-133 (-143, -124); 0.0001*
	Median (range)	0	0
	Discontinuation of factor prophylaxis, n (%)	NR (95)	
Valoctocogene roxaparvovec BMN 270-201 Phase 1/2	**Baseline (N = 6)**		
	Mean (SD)	NR	135.6 (23.0)
	Median (range)		136.5 (104.9-158.5)
	Valoctocogene roxaparvovec 6 years post-dose (N = 6)		
	Mean (SD)	NR	4.7 (NR)
	% Reduction		97
	Mean Change (SD); p-value		NR
	Median (range)		3.5 (NR)
	Discontinuation of factor prophylaxis, n (%)		NR
Emicizumab HAVEN 3 Cohort D Phase 3	**6-month Lead-In (N = 48)**		
	Mean (SD)	602.4 (1822.3)	15.3 (43.6)
	Median (range)	75.5 (0, 473)	3.6 (0, 15)

		Factor use, IU/kg/year	Factor infusions/year
	Emicizumab 24 weeks post-dose (N = 48)		
	Mean (SD)	209.0 (459.8)	7.2 (16.8)
	% Reduction	65	53
	Mean Change (95%CI); p-value	-393.4	-8.1
	Median (range)	19.1 (0, 139)	0.6 (0, 5)
	Discontinuation of factor prophylaxis, n (%)	NR	

95%CI: 95 percent confidence interval, IU/kg: international units per kilogram, n: number, N: total number, NR: not reported, SD: standard deviation

Table D17. Annualized Bleeding Rates: Valoctocogene Roxaparvovec and Emicizumab

		All Bleeds	Treated Bleeds	Treated Spontaneous Bleeds	Treated Joint Bleeds	Treated Target-Joint Bleeds
Valoctocogene roxaparvovec GENEr8-1 Phase 3	**6-month Lead-In (N = 112)**					
	Mean ABR (SD)	NR	4.8 (6.5)	2.0 (3.5)	0.5 (1.6)	2.9 (5.2)
	Median ABR (range)		2.8 (0, 7.6)	0 (0, 3.1)	0	1.1 (0, 3.6)
	N with 0 bleeds (%)	34 (30.4)	36 (32.1)	62 (55.4)	98 (87.5)	50 (44.6)
	Valoctocogene roxaparvovec 52 weeks† post-dose (N = 112)					
	Mean ABR (SD)	NR	0.8 (3.0)	0.4 (1.5)	0.1 (0.4)	0.4 (1.7)
	% Reduction		84.5	81.3	85	85.4
	Mean Change (95%CI); p-value		-4.1 (-5.3, -2.9); 0.0001	-1.6* (NR); NR	-0.4* (NR); NR	-2.5* (NR); NR
	Median ABR (range)		0 (0, 0.4)	0	0	0
	N with 0 bleeds (%)	65 (58.0)	92 (82.1)	98 (87.5)	108 (96.4)	95 (84.8)
Valoctocogene roxaparvovec BMN 270-201 Phase 1/2	**Baseline (N=6)**					
	Mean ABR (SD)	NR	16.3 (15.7)	NR	NR	NR
	Median ABR (range)		16.5 (0-40.0)			
	N with 0 bleeds (%)		1/7 (14)			
	Valoctocogene roxaparvovec 6 years post-dose (N= 6)					
	Mean ABR (SD)	NR	0.8	NR	NR	NR
	% Reduction		95			
	Rate Ratio (95%CI);		-15.5* (NR); NR			

		All Bleeds	Treated Bleeds	Treated Spontaneous Bleeds	Treated Joint Bleeds	Treated Target-Joint Bleeds
	p-value					
	Median ABR (range)		0			
	N with 0 bleeds (%)		4/7 (57)			
Emicizumab HAVEN 3 Group D Phase 3	**Lead-In (N =48)**					
	Mean ABR (SD)	8.9 (5.7, 13.9)	4.8 (3.2, 7.1)	NR	NR	NR
	Median ABR (IQR)	2.7 (0, 9.4)	1.8 (0, 7.6)			
	N with 0 bleeds (%)	32.7 (19.9, 47.5)	40 (26, 55)			
	Emicizumab >24-weeks post-dose (N = 48)					
	Mean ABR (SD)	3.3 (2.2, 4.8)	1.5 (1.0, 2.3)	NR	NR	NR
	% Reduction	63	68			
	Rate Ratio (95%CI); p-value	0.37 (0.2, 0.6); 0.0002	0.32 (0.20, 0.51); <0.001			
	Median ABR (IQR)	1.5 (0, 4.3)	0 (0, 2.1)			
	N with 0 bleeds (%)	NR (44.4)	NR (54)			
	Emicizumab >24 weeks post-dose (N = 63)					
	Mean ABR (SD)	3.3 (2.2, 4.8)	1.6 (1.1; 2.4)	0.5 (0.2, 0.9)	1.2 (0.7, 2.0)	0.6 (0.3, 1.5)
	Median ABR (IQR)	1.5 (0, 4.3)	0.0 (0.0–2.2)	0 (0, 0)	0 (0, 1.6)	0 (0, 0)
	N with 0 bleeds (%)	28 (44.4)	35 (55.6)	52 (82.5)	43 (68.3)	54 (85.7)

*ICER calculation

† Cumulative ABR over 104 weeks for treated bleeds

95%CI: 95 percent confidence interval, ABR: annualized bleeding rate, IQR: interquartile range, N: total number, NR: not reported, SD: standard deviation

Table D18. Durability of Annualized Bleeding Rate of Treated Bleeds: Valoctocogene Roxaparvovec

		Baseline	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
GENEr8-1 Phase 3	**N evaluated**	NR	NR	NR	NYR	NYR	NYR	NYR
	Mean ABR (SD)	4.8 (6.5)	0.9 (NR)	0.7 (NR)				
	% Reduction	reference	81*	85*				
	Mean Change	reference	-3.9*	-4.1*				
	Median (IQR)	2.8 (0, 7.6)	0 (0, 0)	0 (0, 0)				
BMN 270-201 Phase 1/2	**N evaluated**	6	6	6	6	6	6	NR
	Mean (SD)	16.3 (15.7)	1.3 (3.1)	0.2 (0.4)	0.7 (1.6)	1.3 (3.2)	0.7 (1.6)	0.7 (NR)
	% Reduction	reference	92*	99*	96*	92*	96*	96*
	Mean Change	reference	-15*	-16.1*	-15.6*	-15*	-15.6*	-15.6*
	Median (IQR)	16.5 (0, 40.0)	0 (0, 7.6)	0 (0, 1.0)	0 (0, 4.0)	0 (0, 7.9)	0 (0, 4.0)	0 (NR)

* ICER calculation

IQR: interquartile range, N: total number, NR: not reported, NYR: not yet reported, SD: standard deviation

Table D19. Safety: Valoctocogene Roxaparvovec and Emicizumab

		Valoctocogene roxaparvovec GENEr8-1 Phase 3	**Valoctocogene roxaparvovec BMN 270-201** Phase 1/2	**Emicizumab HAVEN 3 Cohort D** Phase 3
N		134	7	63
Follow-up		52-104 weeks	Year 6	~1 year
Adverse Events, n (%)	**Overall**	134 (100)	4 (57.1)	55 (87.3)
	Serious	24 (17.9)	1 (14.3)	8 (12.7)
	Grade 3/4	42 (31.3)	NR	6 (9.3)
Treatment-Related Adverse Events, n (%)	**Overall**	123 (91.8)	0	NR
	Serious	5 (3.7)	0	NR
Mortality, n (%)	**Overall**	1 (0.7)	0	0
	Adverse event-related	0	0	0
Adverse Events of Special Interest				
Headache, n (%)	**Overall**	55 (41)	NR	8 (13)
Arthralgia, n (%)	**Overall**	54 (40)	NR	14 (22)
Nausea, n (%)	**Overall**	50 (37.3)	NR	NR
	Treatment-related	31 (23.1)	NR	NR
Fatigue, n (%)	**Overall**	40 (30)	NR	NR

		Valoctocogene roxaparvovec GENEr8-1 Phase 3	Valoctocogene roxaparvovec BMN 270-201 Phase 1/2	Emicizumab HAVEN 3 Cohort D Phase 3
Infusion-Related Reaction, n (%)	**Overall**	50 (37.3)	0	20 (32)
Influenza, n (%)	**Overall**	NR	NR	5 (8)
Upper Respiratory Tract Infection, n (%)	**Overall**	27 (16.4)	NR	8 (13)
Nasopharyngitis, n (%)	**Overall**	NR	NR	10 (16)
Alanine Aminotransferase Increase, n (%)	**Overall**	119 (88.8)	0	0
	Grade ≥3	11 (8.2)	NR	NR
	Serious	2 (1.5)	NR	NR
	Treatment-related	108 (80.6)	NR	NR
Aspartate Aminotransferase Increase, n (%)	**Overall**	47 (35.1)	NR	0
	Treatment-related	39 (29.1)	NR	NR
Glucocorticoid Use	**n (%)**	106 (79.1)	NR	NR
	Mean dose, mg	8738.6	NR	NR
	Mean duration, days (range)	34.7 weeks	NR	NR
Glucocorticoid-Related Adverse Events, n (%)	**Overall**	81 (60.4)	NR	NR
	Serious	3 (2.2)	NR	NR
Thrombotic Events, N (%)		0	0	0
Factor Inhibitor Development, N (%)		0	0	0
Malignancies, n (%)		0	1 (14.3)	NR
Outcomes not reported: Treatment-related headache, arthralgia, fatigue, infusion-related reaction, influenza, upper respiratory tract infection, nasopharyngitis				

mg: milligram, N/A: not applicable, n: number, N: total number, NR: not reported

Table D20. Health-Related Quality of Life: Valoctocogene Roxaparvovec and Emicizumab

		Baseline Mean (SD)	Post-Treatment Mean (SD)	Mean Change from Baseline (SD); p-value
Hemophilia-Specific Quality of Life Questionnaire For Adults (Haemo-QoL-A)	**Valoctocogene roxaparvovec GENEr8-1 Phase 3 –** Week 52 post-dose			
	Total	75.7 (16.7)	82.2 (15.4)	6.4 (12.0); <0.0001*
	Emotional Impact	78.1 (16.5)	81.1 (16.7)	2.9 (15.5); <0.05
	Treatment Concern	76.2 (25.4)	82.7 (24.5)	6.3 (18.5); <0.001*

		Baseline Mean (SD)	Post-Treatment Mean (SD)	Mean Change from Baseline (SD); p-value
	Role Functioning	78.2 (17.8)	84.5 (15.7)	6.3 (13.4); <0.0001*
	Consequences of Bleeding	73.6 (21.7)	83.4 (19.0)	10.0 (15.3); <0.0001*
	Physical Functioning	70.3(20.8)	77.7(20.8)	7.4(15.4); <0.0001*
	Worry	78.4 (22.7)	84.2 (20.3)	5.8 (20.1); <0.01
	Valoctocogene roxaparvovec BMN 270-201 Phase 1/2 – Year 5 post-dose			
	Total	71.9 (16.6)	82.2 (18.1)	10.3 (13.6); NR
EuroQol-5 Dimension (EQ-5D)	**Valoctocogene roxaparvovec GENEr8-1 Phase 3** – 52 weeks post-dose			
	EQ-5D-5L‡	0.78 (0.17)	0.82 (NR)	0.04 (0.16); 0.002*
	EQ-5D-VAS†	80.1 (15.3)	85.6 (NR)	4.5 (13.3); 0.0002*
Haemophilia Quality of Life Questionnaire for Adults (Haem-A-Qol)§	**Emicizumab HAVEN 3 Phase 3** – Week 73			
	Total	31.5	21.9	-9.6 (30.5%); NR
	Physical Health	38.8	27.7	-11.1 (28.6%); NR

* Statistically significant
† Scores range from 0 to 100; higher scores indicate better quality of life
‡ Scores range from 0 to 1; higher scores indicate better quality of life
§ Scores range from 0 to 100; lower scores indicate better quality of life
NR: not reported, SD: standard deviation

D3. Ongoing Studies

Table D21. Ongoing Studies

Title / Trial Sponsor	Study Design	Treatment Arms	Patient Population	Outcomes	Estimated Completion Date*
Etranacogene Dezaparvovec					
HOPE-B: Trial of AMT-061 in Severe or Moderately Severe Hemophilia B Patients CLS Behring NCT03569891	Open-label, single-dose, multi-center, multinational trial Estimated enrollment: N = 56	**Arm 1**: Single infusion of AMT-061 (etranacogene dezaparvovec)	**Inclusions** - Adult male aged 18 years old or above - Diagnosed with Hemophilia B without inhibitors, classified as severe or moderately severe, and are currently on factor IX prophylaxis - Must have more than 150 days previous exposure with factor IX protein **Exclusions** - No history of factor IX inhibitors	**Primary** - Annualized bleeding rate [52 weeks] **Secondary** - Factor IX activity levels [up to 18 months] - Use of Factor IX replacement therapy [52 weeks] - Adverse events [5 years]	**Primary:** Completed **Study**: March 2025

			- Treated with gene therapy before		
Valoctocogene Roxaparvovec					
Study to Evaluate the Efficacy and Safety of Valoctocogene Roxaparvovec, With Prophylactic Steroids in Hemophilia A (GENEr8-3) BioMarin Pharmaceutical NCT04323098	Phase 3b, Single Arm, Open-Label Study Estimated enrollment: N = 20	**Arm 1**: Single administration of valoctocogene roxaparvovec at a dose of 6E13 vg/kg with prophylactic corticosteroids	**Inclusions** - Adult male aged 18 years old or above - Diagnosed with hemophilia A and residual FVIII levels ≤ 1 IU/dL - Must have been on prophylactic therapy for at least 12 months prior to study - No history of FVIII inhibitor - Exposed or treated to FVIII concentrates or cryoprecipitate for a minimum of 150 days **Exclusions** - Pre-existing antibodies to AAV5 capsid - Patients with HIV infection or a history of hepatic malignancy - Significant renal dysfunction or liver dysfunction	**Primary** - Change in median FVIII activity [52 weeks] **Secondary** - Change in the annualized utilization (IU/kg) of exogenous FVIII replacement therapy or emicizumab [52 weeks] - Change in the annualized number of bleeding episodes requiring FVIII replacement treatment [52 weeks] - Haemo-QoL-A [52 weeks]	**Primary:** January 2023 **Study:** January 2027
Safety, Tolerability, and Efficacy Study of Valoctocogene Roxaparvovec in Hemophilia A With Active or Prior Inhibitors BioMarin Pharmaceutical NCT04684940	Phase 1/2, Single Arm, Open-Label Study Estimated enrollment: N = 20	**Arm 1**: Single administration of valoctocogene roxaparvovec at a dose of 6E13 vg/kg	**Inclusions** - Adult male aged 18 years old or above - Diagnosed with hemophilia A and residual FVIII levels ≤ 1 IU/dL - Must have been on prophylactic or on-demand therapy in the last 12 months - History of a positive FVIII inhibitor with the first positive result in the last 12 months **Exclusions** - Pre-existing antibodies to AAV5 capsid - Patients with HIV infection or a history of hepatic malignancy - Significant renal dysfunction or liver dysfunction	**Primary** - Adverse events [60 months] **Secondary** - Change in median FVIII activity [60 months] - Absence of recurrence of Factor VIII inhibitors [60 months] - Change in the annualized utilization (IU/kg) of hemophilia therapy [60 months] - Change in the annualized number of bleeding episodes requiring exogenous hemophilia therapy [60 months]	**Primary:** February 2029 **Study:** February 2029

Gene Therapy Study in Severe Hemophilia A Patients With Antibodies Against AAV5 (270-203) **BioMarin Pharmaceutical** NCT03520712	Phase 1/2, Single Arm, Open-Label Study Estimated enrollment: N = 10	**Arm 1**: Single administration of BMN270 (valoctocogene roxaparvovec) at a dose of 6E13 vg/kg	**Inclusions** - Adult male aged 18 years old or above - Diagnosed with hemophilia A and residual FVIII levels ≤ 1 IU/dL - Must have been on prophylactic therapy for at least 12 months prior to study - No history of FVIII inhibitor - Detectable pre-existing antibodies against the AAV5 vector capsid **Exclusions** - Evidence of covid-19 or any immunosuppressive disorder active infection except for HIV - Chronic or active hepatitis B or C - Liver dysfunction - Active malignancy, except non-melanoma skin cancer, or history of hepatic malignancy	**Primary** - Adverse events [61 months] **Secondary** - FVIII activity at or above 5 IU/dL [26 weeks] - Use of exogenous FVIII replacement therapy [61 months] - Number of bleeding episodes requiring exogenous FVIII therapy [61 months]	**Primary:** November 2027 **Study:** November 2027

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

* Primary completion date refers to when the last participant will be examined or receive the intervention. Study completion date refers to when final data on all participants is collected.

dL: deciliter, FVIII: factor VIII, HIV: human immunodeficiency virus, IU: international units, kg: kilogram, N: total number, vg: vector genome

E. Long-Term Cost-Effectiveness: Supplemental Information

E1. Detailed Methods

Table E1. Impact Inventory

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

NA: not applicable

Adapted from Sanders et al[61]

Description of evLY Calculations

The equal value life year (evLY) considers any extension of life at the same "weight" no matter what treatment is being evaluated or what population is being modeled. Below are the stepwise calculations used to calculate the evLY.

1. First, we attribute a utility of 0.851, the age- and sex-adjusted utility of the general population in the US that are considered healthy.[62]
2. We calculate the evLY for each model cycle.
3. Within a model cycle, if using the intervention results in additional life years versus the primary comparator, we multiply the general population utility of 0.851 with the additional life years gained (ΔLY gained) within the cycle.
4. The life years shared between the intervention and the comparator use the conventional utility estimate for those life years within the cycle.
5. The total evLY for a cycle is calculated by summing steps 3 and 4.
6. The evLY for the comparator arm is equivalent to the QALY for each model cycle.
7. The total evLYs are then calculated as the sum of evLYs across all model cycles over the time horizon.

Finally, the evLYs gained is the incremental difference in evLYs between the intervention and the comparator arm.

Target Population

The population of focus for the economic evaluation of etranacogene dezaparvovec (Model 1) was adult males (age 18 and over) with severe hemophilia B without inhibitors who require prophylaxis.

The population of focus for the economic evaluation of valoctocogene roxaparvovec (Model 2) was adult males (age 18 and over) with severe hemophilia A without inhibitors who require prophylaxis.

Treatment Strategies

Model 1 Intervention

- Etranacogene Dezaparvovec

Model 2 Intervention

- Valoctocogene Roxaparvovec

Comparators

Model 1 Comparator

- Factor IX

Model 2 Comparator

- Emicizumab

E2. Model Inputs and Assumptions

Below is a list of key model choices common to both models:

- The structures of the models were based around the Pettersson score (PS). This allowed for longer model cycles, reducing computational complexity, while still accounting for bleeds each year as well as the development of arthropathy and the possibility of requiring surgery.
- Bleed rates determined transition rates across PS, and were key in projecting costs, and utilities in the model.
- Given treatment, mortality with hemophilia A or B is similar to the US average and there are no differential effects on mortality across the treatments. For mortality we use CDC based mortality rates adjusted (exponentially) to reflect per cycle probabilities of death.
- The models used 6-month cycles. This was the longest standard cycle that allowed for reasonable transition rates between PS counts each cycle, given the expected bleeding rates possible in the models.
- Costs and effects were discounted using a rate of 3%.
- Utilities derived from the published literature were weighted by the time spent in each health state.[33-37] The models included separate utilities for different types of bleed events, varying baseline utility by age and arthropathy, and utility associated with requiring surgery.
- The models included all direct treatment costs associated with each individual regimen, including drug acquisition costs and non-pharmacy costs (including all medical expenses associated with bleeds).

- All costs prior to 2021-were adjusted for inflation following methods outlined in the ICER reference case so that all cost inputs and outputs in the model reflect 2021 US dollars.[38,39]All costs prior to 2021-were adjusted for inflation following methods outlined in the ICER reference case so that all cost inputs and outputs in the model reflect 2021 US dollars.[38,39]

Key model choices specific to the hemophilia B model:

- Factor IX dosing and costs were based on available representative doses of those drugs provided by the manufacturers of etranacogene dezaparvovec.
- Bleed rates for etranacogene dezaparvovec will be taken from the HOPE trial.[9] Bleed rates for etranacogene dezaparvovec will be taken from the HOPE trial.[9] Available evidence on factor IX levels across time were used to consider the impact of declining efficacy across time for etranacogene dezaparvovec on bleed rates. Here projected factor activity levels below 5 IU/mL were assumed to lead to 5% of patients switching to factor IX and at levels below 1 IU/mL, all patients switched to factor IX. When projected bleeds for etranacogene dezaparvovec are higher than the initial rates, the projected rates are used.
- Bleed rates for factor IX were also based on baseline data from the HOPE trial.
- Etranacogene dezaparvovec was associated with a fixed utility gain of 0.03 per cycle as long as patients did not switch therapies based on data submitted by CSL Behring.
- Steroid use in the first cycle is modeled using prednisone and a disutility of 0.03.[9]

Key model choices specific to the hemophilia A model:

- Bleed rates across time for valoctocogene roxaparvovec in the hemophilia A model were derived from available data on factor levels seen in patients on that treatment and literature-based estimates of bleed rates across factor levels. At projected factor activity levels below 5 IU/mL, 5% of valoctocogene roxaparvovec patients were assumed to switch to emicizumab prophylaxis. At projected factor activity levels below 1 IU/mL, all valoctocogene roxaparvovec patients were assumed to switch to emicizumab.
- Bleed rates were taken from the Haven 3 trial for emicizumab.[22]
- Proportions of all bleeds relative to treated bleeds in the HAVEN 3 trial along with proportions of all bleeds that are joint bleeds in the HAVEN 3 and POTTER trials were used to estimate different types of bleeds relative to treated bleeds for valoctocogene roxaparvovec.
- Factor VIII dosing and costs were based on two representative treatments, Advate for standard half-life, and Eloctate for extended half-life, using doses of those drugs consistent with patients treated with those treatments in US hemophilia treatment centers affiliated with ATHN.
- Valoctocogene roxaparvovec was associated with a fixed utility gain of 0.01 per cycle as long as patients did not switch therapies based on data submitted to ICER.[42] .

- Steroid use is modeled for the first two cycles based on prednisone costs and a disutility of 0.03.[17]

See Table E2 for assumptions common to both models and specific assumptions for the hemophilia B model in Table E3 and specific assumptions for hemophilia A in Table E4.

Table E2. Model Assumptions Common to Both Models

Assumption	Rationale
Annual bleed rates are equivalent regardless of the degree of arthropathy.	Data on the relative occurrence of bleed events pre- and post-arthropathy are limited. Increasing bleed rates due to arthropathy are explored in a scenario analysis.
Pettersson scores (representing joint arthropathy development) increase as a function of joint bleeds (treated and/or untreated) over time at different rates for patients over and under the age of 25.	Pettersson scores have most recently been reported to increase by one point for every 36.52 joint bleeds (treated and/or untreated) in patients under 25 and by one for every 6.52 joint bleeds for patients over 25.[43]
All patients are assumed to be male, and patient weight and background mortality will be based on US male population averages.	Hemophilia is an X-linked recessive disease primarily affecting males. Females with hemophilia typically have less severe disease. We assume that prophylaxis of hemophilia will not substantially impact weight or mortality.
The utilities associated with a bleed are applied for two days. After two days we assume the bleed state utility is an average of the no bleed and bleed values for the remainder of a week to reflect that the impact of the bleed on utility lingers after the bleeding stops.	The duration of a bleed is estimated to be two days. However, the impact of a bleed likely lingers beyond bleed duration and treatment time. The number of days per week for bleed utilities is varied in a scenario analysis.
Bleed disutilities will be derived from patients with inhibitors as opposed to patients without inhibitors and hence the bleed disutility was assumed to be the same for those without inhibitors as seen in those with inhibitors.	The bleed disutilities in the population with inhibitors could potentially be greater than those without inhibitors. Thus, the treatment effect of emicizumab and valoctocogene roxaparvovec may be slightly overestimated. Sensitivity analyses around these bleed utilities were assessed.
Cost per treated bleed event is the same for all comparators within each model.	We have not seen evidence to support different on-demand treatment costs for patients on different forms of prophylaxis.

Table E3. Assumptions Specific to Hemophilia B

Assumption	Rationale
Several cost and disutility values associated with bleeds in hemophilia B are assumed to be the same as those seen in hemophilia A patients.	Per bleed costs and disutilities are not directly available in the literature for hemophilia B patients. Discussions with patients and clinical leaders suggest similar types and severity of bleeds in hemophilia B as in hemophilia A.

Table E4. Assumptions Specific to Hemophilia A

Assumption	Rationale
Different types of bleeds relative to treated bleeds for valoctocogene roxaparvovec are modeled based on the emicizumab arm of the HAVEN 3 trial. [22] Joint bleeds are assumed to be the same percentage of all bleeds for each comparator using a simple average of rates of total joint bleeds to all bleeds seen in the various arms of the HAVEN 3 trial (provided by Genentech) and the proportion seen in the POTTER trial (resulting in 0.66 as the proportion used).	Best available data to relate factor levels to bleeds only exists for treated joint bleeds. The chosen method to project other types of bleeds was evidence based and most consistent with any projections for other treatments in the model.
An outcome-based warranty with the following features was incorporated in the full cost-offset analysis. For an anticipated potential of 2% of patients that fail treatment each cycle in the first four years would receive reimbursement payments. These payments would substantially cover prophylaxis costs from the time of failure through the end of year four.	The warranty seemed like a very realistic option for reimbursing patients that fail the treatment so it was incorporated in the full cost-offset analysis.

Model Inputs

Clinical Inputs

Clinical inputs to the model will be based on clinical trial data and related literature.

Bleed Rates in Model 1

Bleed rates for factor IX were taken from baseline data in the HOPE trial provided by CSL Behring and held constant. These include rates of total and treated bleeds overall as well as total and treated joint bleeds. For etranacogene dezaparvovec, the bleed rates seen in months 7-18 of the HOPE trial will be used with adjustment for evidence on declines in factor IX levels across time (see Tables E5 and E6 and Figure E1 below). Linear regression on available factor IX levels from patients

with consistent data across the longest time period were used to project factor IX levels across time and bleed rates seen in patients with hemophilia A with low factor VIII levels with a literature-based adjustment were used to project increasing bleed rates as factor IX levels decrease. Specifically using factor IX levels in place of factor VII and adjusting projected bleeds per factor level by 0.6/1.4, when projected bleeds (see more detail on projections below) from the respective levels of factor IX are higher than those in the HOPE trial for etranacogene dezaparvovec then those were used. Further, when factor IX levels reach 5 IU/mL, 5% of etranacogene dezaparvovec patients initiate factor IX, and when the projected factor IX levels reached 1 IU/mL, all in that arm were modeled to initiate factor IX therapy. Finally, in the initial cycle bleeds for the etranacogene patients assumed 3 months with factor IX bleed rates and 3 months with the 7–18-month bleed rates for etranacogene dezaparvovec in the HOPE trial. Further, when factor IX levels reach 5 IU/mL, 5% of etranacogene dezaparvovec patients initiate factor IX, and when the projected factor IX levels reached 1 IU/mL, all in that arm were modeled to initiate factor IX therapy. Finally, in the initial cycle bleeds for the etranacogene patients assumed 3 months with factor IX bleed rates and 3 months with the 7–18-month bleed rates for etranacogene dezaparvovec in the HOPE trial.

Adverse events in Model 1

We include costs based on prednisone and a small disutility for the expected use of steroids in the first cycle based on steroid use seen in trials.[9] We also include a scenario analyses with a much higher estimate of potential AE cost of $2200 per cycle for etranacogene dezaparvovec for 1 cycles.

Table E5. Initial Bleed Rates in Model 1

Drug	All Bleeds	All Joint Bleeds	Treated Non-Target Joint Bleeds	Treated Target Joint Bleeds	Source
Etranacogene Dezaparvovec	1.51	0.51	0.40	0.44	Hope Trial[9]
Factor IX	4.19	2.35	1.52	2.13	Hope Trial[9]

See Figure E2 and Table E6 below to see projections of factor IX levels across time.

Figure E1. Projected Factor IX Levels Across Cycles

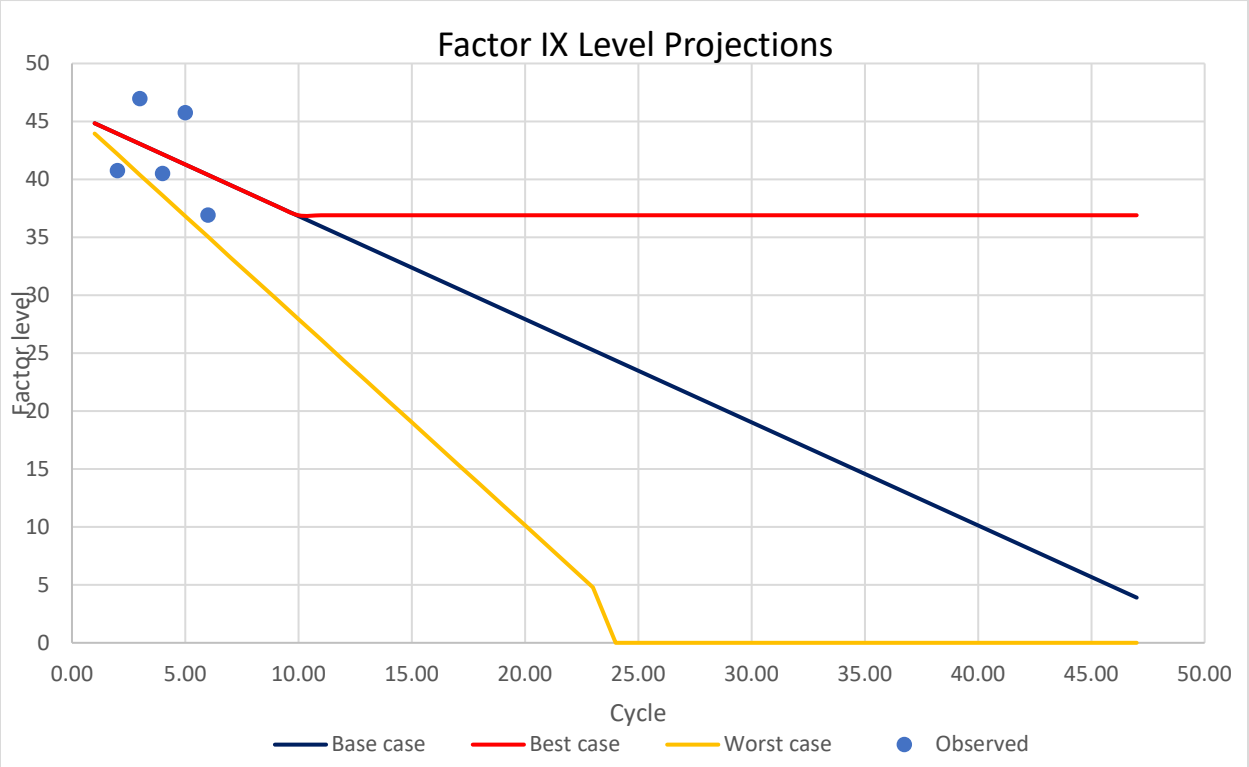


Table E6. Bleed Rates in Hemophilia A for Selected Factor VIII Levels Used to Project Bleeds

Factor Level*	All Bleeds	Joint Bleeds	Untreated Bleeds	Treated Non-Target Joint Bleeds	Treated Target Joint Bleeds
11-40	0.451	0.297	0.225	0.104	0.121
9	1.936	1.277	0.968	0.447	0.521
7	2.311	1.525	1.156	0.533	0.622
4	4.102	2.714	2.051	0.947	1.104
1-3	7.280	4.805	3.640	1.680	1.960

*In model 2, factor projections are not used until they are higher than those seen in the GENREr8-1 data. For model 1, bleed rates will be adjusted by 0.6/1.4 and rates below the initial bleed rates seen in the HOPE trial will not be used (this happens at factor level = 4).

Bleed Rates in Model 2

Treated bleed rates for valoctocogene roxaparvovec were modeled based on the GENEr8-1 trial and available evidence of treated joint bleed rates across factor levels seen in moderate and mild hemophilia patients by den Uijl et al (see Table E6 above).[40] Treated bleed rates for valoctocogene roxaparvovec were modeled based on the GENEr8-1 trial and available evidence of treated joint bleed rates across factor levels seen in moderate and mild hemophilia patients by den Uijl et al (see Table E6 above).[40] To begin, we used average bleed rates seen in patient level data in the GENEr8-1

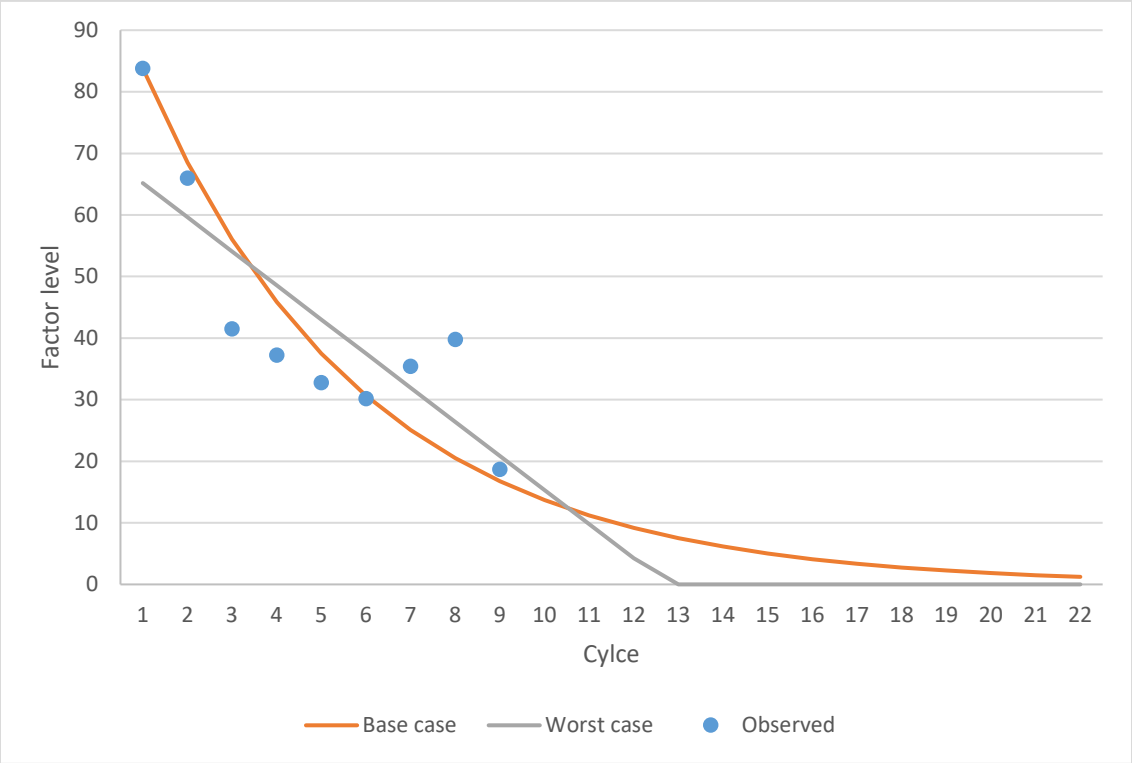
trial but with the following assumptions. To be most consistent with the value-based contract proposed by BioMarin we had 2% of the patients with the highest ABR drop out of the data each year for the first four years. In cycle zero we used the average as seen in the GENEr8-1 data for three months for valoctocogene roxaparvovec and 3 months of the emicizumab bleed rate. Then we began having high ABR patients exit and using the remaining patients, we calculated the ABR for valoctocogene roxaparvovec from the remaining patients and used the HAVEN 3 and Potter trial based relative proportions of different types of bleeds from there. We also used projected bleeds based on projected factor levels. To project treated joint bleed rates, median one-stage factor VIII levels of high dose patients from BioMarin were combined with estimated rates of treated joint bleeds by factor level in den Uijl et al.[40] In addition, to balance these estimates with lower than usual bleed rates seen in the trials, patients with factor activity levels between 1 and 3 IU/mL were assigned the bleed level of those with 3 IU/mL. Further, we averaged across the tail of the bleed rates for factor levels of 11 IU/mL and up and assigned that to all those over 11 IU/mL and made a slight adjustment (i.e. changed from 0.78 to 0.80) to a non-monotonic portion of the relationship between factor levels and bleeds at factor levels less than 11 IU/mL after digitizing figure 2 from den Uijl et al.[40] Declines across time in patient factor levels were projected forward based on a fitted exponential survival curve to a weighted average of the available data on factor levels in patients from the trials omitting some data with less than full samples (see Figure E2.2 below) as well as linear projections from these data for a scenario. When bleed rates from these projections became higher than those projected based on the GENEr8-1 data with dropouts we used the projected rates. Further, once patients were projected to be at factor levels below 5 IU/mL (cycle 16), 5% of the patients were assumed to switch treatment, and then once the patients were projected to be at less than 1 IU/mL (cycle 24), all patients were assumed to initiate treatment with emicizumab. Table E7 below illustrates the range of bleed rates for valoctocogene roxaparvovec in the model.

Table E7. Bleed Rates in Model 2

Drug	All Bleeds	All Joint Bleeds	Treated Non-Target Joint Bleeds	Treated Target Joint Bleeds
Emicizumab	3.00	1.98	0.69	0.81
Valoctocogene Roxaparvovec Year 2	0.49	0.33	0.13	0.11
Valoctocogene Roxaparvovec Year 11	7.28	4.82	1.68	1.95
Valoctocogene Roxaparvovec Year 20	3.00	1.98	0.69	0.81

See Figure E2 below for projections of factor VIII levels across time. Note that the optimistic scenario used the same curve shown here but used bleed rates associated with a factor level of 5 IU/mL for all levels below 5 IU/mL.

Figure E2. Projected Factor VIII Levels Across Cycles for Model 2



Adverse Events in Model 2

We include costs based on prednisone and a small disutility for the expected use of steroids in the first cycle based on steroid use seen in trials.[17] We also include a scenario analysis with a much higher AE cost of $2200 for two cycles for valoctocogene roxaparvovec.

Transition Probabilities

Example transition rates for model 2 corresponding to the bleed rates of the drugs are shown in Table E8 and are based on numbers described above related to bleed rates and PS by age in the POTTER trial. The rates changed across time for valoctocogene roxaparvovec based on the projections of factor levels described above.

Table E8. Example Per Cycle Transition Probabilities Across Pettersson Scores in Model 2

Drug	Age 18-24	Age 25 and Over
Emicizumab	0.027	0.141
Valoctocogene Roxaparvovec Year 1	0.01	N/A
Valoctocogene Roxaparvovec Year 2	0.008	N/A
Valoctocogene Roxaparvovec Year 20	N/A	0.141

Valoctocogene Roxaparvovec has relatively high bleed rates in year 1 as the treatment is assumed to take a few months before it has an impact.

Discontinuation

We did not model any discontinuation for either intervention due to each being one-time gene therapies. The models also did not include discontinuation in the comparator arms as a conservative approach and due to lack of available data on discontinuation rates. Patients not on the gene therapy would require lifelong treatment on factor IX in the hemophilia B model and on emicizumab in the hemophilia A model.

Mortality

Age-specific all-cause mortality in both models will be sourced from the CDC life tables for males (adjusted to reflect per cycle probabilities of death) which are representative of the male population in the US.[64] Prophylaxis for hemophilia A in patients without inhibitors has not been demonstrated to decrease mortality,[65] there is no evidence of differential mortality effects in hemophilia B, and the mortality rates seen over recent decades may not apply now that there are effective therapies for HIV and hepatitis C and new cases related to factor VIII or factor IX contamination are unlikely to occur.[64] Prophylaxis for hemophilia A in patients without inhibitors has not been demonstrated to decrease mortality,[65] there is no evidence of differential mortality effects in hemophilia B, and the mortality rates seen over recent decades may not apply now that there are effective therapies for HIV and hepatitis C and new cases related to factor VIII or factor IX contamination are unlikely to occur. As such, there is little evidence to suggest a differential mortality effect across options for prophylaxis in either model.

Serious Adverse Events

The HOPE trial did not demonstrate evidence of serious adverse events associated with treatment. Serious adverse event data reported in the HAVEN trials for emicizumab, particularly in HAVEN 3, were not significantly associated with the drug. For valoctocogene roxaparvovec, we accounted for the costs of treating elevations in alinine aminotransferase levels seen in the vast majority of patients from the GENEr8-1 trial but given at most very small proportions of other SAEs they were not included.[17] We also include a scenario analysis with a higher cost estimate for SAEs in the gene therapies based on cost estimates provided by Genentech.

Utilities

Health state utilities in both models will be derived from published literature sources and applied to the relevant health states. Baseline utility will be taken from results of EQ-5D utilities based on responses from hemophilia patients broken out by age and degree of arthropathy, found in O'Hara et al (Table E9).[44] All of the disutilities associated with bleeds and with surgery used in the models are measured in patients with hemophilia A using the EQ-5D. We will use the same health state utility values across treatments evaluated in both models. Utility in the surgery state will be modelled using one month of having a time-tradeoff utility found in a general hip replacement pre-surgery patient group reported in the literature in 1993 (0.32), and 5 months with utility corresponding to a PS of 14-27 and the age of the patient getting surgery in the model.

Table E9. Health State Utilities in the Models

Age	Pettersson 14-27	Surgery*	Source
18-30	0.82	0.72	O'Hara 2018[66], Laupacis 1993[45]
31-40	0.74	0.65	O'Hara 2018[66], Laupacis 1993[45]
41-50	0.69	0.61	O'Hara 2018[66], Laupacis 1993[45]
51-60	0.63	0.56	O'Hara 2018[66], Laupacis 1993[45]
61 and over	0.54	0.48	O'Hara 2018[66], Laupacis 1993[45]

*The utility of surgery is based on one month of utility at 0.32 and 5 months of utility in Pettersson 14-27.

Disutilities by bleed type will be estimated based on differences in utilities reported during bleed episodes versus when having no bleeds, measured in patients with hemophilia A with inhibitors. As stated above, bleed-associated disutilities for treated target joint bleeds and treated non-target joint bleeds will be applied in full for two days, followed by an average of "No Bleed" and "Bleed" utilities for five days (Table E10).[33] In reality, bleed duration will vary depending on severity of the bleed, time to treatment, and other variables including location, so we will vary these assumptions in a scenario analysis.[33]

Table E10. Bleed-Related Disutilities

Bleed Type	Disutility per Cycle*	Source
Bleed Not Into a Target Joint	-0.002	Neufeld 2012[33]
Target Joint Bleed	-0.003	Mazza 2016[35]

*Based on -0.16 and -0.28 disutility per day for a treated bleed and treated joint bleed, respectively.

In addition, and fixed utility gain of 0.03 was used for etranacogene dezaparvovec and a gain of 0.01 was used for valoctocogene roxaparvovec in their respective models based on data provided by CSL Behring and from a data analysis by Benton and Shi [42].

Economic Inputs

Drug Acquisition Costs

Model 1

Dosing of etranacogene dezaparvovec as well as for the selected factor IX products in the market basket comes from the HOPE trial and available real world doses of factor IX products in the US provided by CSL Behring. Prophylactic use of factor IX was projected to last a lifetime. In scenarios where the efficacy of etranacogene dezaparvovec was projected to last less than a lifetime it is assumed that patients will switch to factor IX. The market basket of factor IX consists of 32.26% Alprolix, 32.26% Benefix, 33.33% Idelvion, and 2.15% Rebinyn which was derived from IQVIA data provided by CSL Behring. Dosing of all these drugs varies by weight and will be modeled based on average weight by age for males in the US. For treated bleeds in the hemophilia B model, a market basket approach along with the most common dose in each product was used with costs reflecting one administration per bleed. See Table E11 for specific doses used in model 1.

Table E11. Drug Doses Used in Model 1

Drug	Dose	Schedule	Source
Etranacogene Dezaparvovec	2.0 X 10^13 gene copies/kg	Once	HOPE Trial via CSL Behring
Alprolix	52.00 IU/kg	90% weekly, 10% every 10 days	Monthly Index of Medical Specialties
Benefix	81.67 IU/kg	50% every 3 days, 50% every 4	Monthly Index of Medical Specialties
Idelvion	37.66 IU/kg	80% (dose every 7 days at 35 IU/kg); 8% (dose every 7 days at 50 IU/kg); 8% (dose every 10 days at 75 IU/kg); 3% (dose every 14 days at 75 IU/kg); 1% (dose every 21 days at 100 IU/kg)	Monthly Index of Medical Specialties
Rebinyn	40.00 IU/kg	Weekly	Monthly Index of Medical Specialties

IU: international unit, kg: kilograms

Model 2

Utilization of emicizumab will be assumed to be the same as seen in HAVEN 3.[22] Utilization for valoctocogene roxaparvovec will be tied to the highest dose seen in the available trials, as that dose was associated with the largest treatment effects across time. For valoctocogene roxaparvovec, a dose of $6x10^{13}$ vg/kg will be used which has been found to have the best efficacy in available trials. For emicizumab, 3 mg/kg every week for the first month and then 3 mg/kg every other week after the first month will be used which is consistent with the best efficacy seen in the Haven 3 trial.[22] A lifetime treatment duration is assumed.[22] Dosing of these drugs varies by weight, and in both models, patient weight will be modeled based on average weight by age for males in the US.

For treated bleeds in the hemophilia A model, factor VIII use will be assumed to be 50.4 IU/kg per bleed, and we will use a market basket (71.18% standard half-life, and 28.82% extended half-life). Drug utilization for factor VIII is based on a market basket approach using proportions of different types of factor VIII treatments seen in recent market basket data provided by the American Thrombosis and Hemostasis Networks (ATHN), representative treatments of each type, and typical doses for those products. Specifically, Advate® was selected to represent standard half-life treatment, used by 71.18 % of the patients, and Eloctate® was selected to represent extended half-life treatment, used by 28.82% of patients and doses of 118.2 IU/kg for Advate and 111.2 IU/kg for Eloctate will be used based on average doses seen in ATHN data in 2019 for first time prophylactic treatment regimens at the underlying US hemophilia treatment centers that provide data to the ATHN and which were also consistent with the labels, input from clinical experts, and a recently published economic models.[67-69] Dosing of these drugs varies by weight and in both models patient weight by age will be modeled based on average weight by age for males in the US. Finally, we used Prednisone 60mg for two months for the proportion of patients (85%) expected to experience elevations in alinine aminotransferase levels.

Cost Inputs

All costs used in the model were updated to 2021 dollars.

Non-Drug Costs

Non-Drug Per Bleed Costs

Non-pharmacological costs from Shrestha et al. will be used to inform the direct non-pharmacy related medical costs associated with treated bleeds and treated joint bleeds (see Table E12).[70] The models purposely use per-bleed costs here to focus on cost reductions associated with reductions in bleeds will be used to inform the direct non-pharmacy related medical costs associated with treated bleeds and treated joint bleeds (see Table E12).[70] Estimates of these costs were available for three age groups: < 18, 18 to 45, and > 45 years old. Shrestha et al. examined mostly patients not on prophylactic treatment, and the non-pharmacy costs per bleed were not statistically significantly different for those on prophylaxis for patients aged 18 and over. Some fixed costs, for example those associated with diagnosis of hemophilia B or hemophilia A, are ignored in the model knowing that they would likely be the same across treatments within each model and would not affect incremental costs.

Table E12. Non-Drug Costs per Bleed by Age

Age (years)	Cost	Source
18-45	$4,832.33	Shrestha 2017[70]
>45	$7,197.87	Shrestha 2017[70]

Added Cost of Arthropathy

In addition to the per-bleed costs, published findings of increased utilization associated with arthropathy will be incorporated into both models. Specifically, reported differences in annual use of outpatient physician visits, outpatient nurse visits, as well as joint-related tests including X-ray and magnetic resonance imaging will be used along with CMS physician fee schedule costs for 2018, inflated to 2022 (see Table E13).

Table E13. Costs per Cycle of Arthropathy and Surgery

State	Cost	Source
Arthropathy (PS 14-27)	$648.90 per cycle based on office visits and joint related tests	O'Hara 2018[44], CMS Fees[71]
Surgery	Above plus $46,931.65	Earnshaw 2015[72]

Costs are inflated here to 2021.

Societal Costs

Costs associated with lost time from work for patients and caregivers will be estimated based on a burden of illness analysis by Zhou et al.[73] The costs will be inflated from 2011 to 2019 by using the total compensation per hour for civilian workers from the Bureau of Labor Statistics. The calculated societal cost per treated bleed is $1,235.30.

E3. Results

Full Cost-Offset Results

Model 1

Table E14 below shows the traditional full cost-offset results for model 1 with a price for etranacogene dezaparvovec of $3,500,000. Both treatment arms are projected to have extremely high lifetime costs, with etranacogene dezaparvovec having lower costs and slightly higher quality adjusted life years. Etranacogene dezaparvovec was also associated with lower bleeds. Life years are the same across treatments and consequently evLYs are the same as QALYs.

Table E14. Results for the Full Cost-Offset Analysis for Etranacogene Dezaparvovec Compared to Factor IX

Treatment	Drug Cost	Total Cost	Bleeds	QALYs	Life Years	evLYs
Etranacogene Dezaparvovec	$8,500,000	$9,454,000	182	20.03	27.13	20.03
Factor IX	$14,029,000	$15,797,000	247	19.39	27.13	19.39

Table E15 below shows the incremental results. Etranacogene dezaparvovec and factor IX had identical life years and etranacogene dezaparvovec was projected to be a dominant treatment with lower costs and higher QALYs and evLYs.

Table E15. Incremental Cost-Effectiveness Ratios for the Full Cost-Offset Analysis

Treatment	Comparator	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained	Cost per Bleed Averted
Etranacogene dezaparvovec	Factor IX	Dominant	Undefined	Dominant	Dominant

evLYG: equal value life year gained, QALY: quality-adjusted life year

Model 2

Table E16 below shows the traditional full cost-offset analysis results for model 2 with a placeholder price for valoctocogene roxaparvovec of $2,500,000. Both treatment arms are projected to have extremely high lifetime costs with valoctocogene roxaparvovec, having lower costs and slightly higher quality adjusted life years. Valoctocogene roxaparvovec, was also associated with slightly lower bleeds. Life years are the same across treatments and consequently evLYs are the same as QALYs.

Table E16. Results for the Full Cost-Offset Analysis for Valoctocogene Roxaparvovec Compared to Emicizumab

Treatment	Drug Cost	Total Cost	Bleeds	QALYs	Life Years	evLYs
Valoctocogene Roxaparvovec	$13,635,000*	$14,076,000	171	19.64	27.13	19.64
Emicizumab	$17,492,000	$18,084,000	177	19.54	27.13	19.54

*Based on a placeholder cost for valoctocogene roxaparvovec of $2,500,000

Table E17 below shows the incremental results. Valoctocogene roxaparvovec and emicizumab had identical life years, and valoctocogene roxaparvovec was projected to be a dominant treatment with lower costs, very slightly lower bleeds and higher QALYs and evLYs.

Table E17 Incremental Cost-Effectiveness Ratios for the Full Cost-Offset Analysis

Treatment	Comparator	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained	Cost per Bleed Averted
Valoctocogene Roxaparvovec	Emicizumab	Dominant	Undefined	Dominant	Dominant

evLYG: equal value life year gained, QALY: quality-adjusted life year

E4. Sensitivity Analyses

To demonstrate effects of uncertainty on both costs and health outcomes, we varied conducted one way and probabilistic sensitivity analyses.

Model 1

Figures E3 and E4 and Tables E19 and E20 below show the tornado diagrams for the incremental costs and then QALYs of etranacogene dezaparvovec versus FIX in model 1. For costs the per year cost of FIX had the largest impact, but for all ranges of all the inputs the incremental costs of etranacogene dezaparvovec were substantially lower. The fixed utility gain of etranacogene dezaparvovec had the biggest impact on QALYs in the one way analyses. In all ranges of all variables in the one way analyses the QALYs were higher for etranacogene dezaparvovec.

Figure E3. Tornado Diagram on Incremental Costs of Etranacogene Dzaparvovec versus FIX

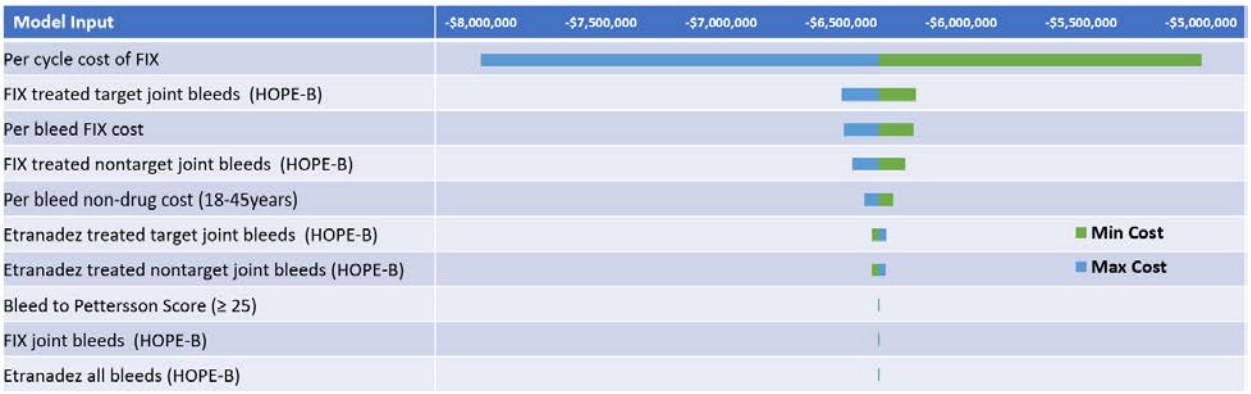


Table E18. Inputs and Results for Etranacogene Dezaparvovec versus FIX cost Tornado Diagram

Inputs	Low Input Value	High Input Value	Min Cost	Max Cost
Per cycle cost of FIX	$177,312	$295,520	-$4,083,938	-$8,601,462
FIX treated target joint bleeds (HOPE-B)	1.5975	2.6625	-$6,188,579	-$6,496,822
Per bleed FIX cost	$8,177	$13,629	-$6,197,471	-$6,487,930
FIX treated nontarget joint bleeds (HOPE-B)	1.14	1.9	-$6,232,717	-$6,452,684
Per bleed non-drug cost (18-45years)	$3,624	$6,040	-$6,283,298	-$6,402,103
Etranadez treated target joint bleeds (HOPE-B)	0.33	0.55	-$6,372,846	-$6,312,554
Etranadez treated nontarget joint bleeds (HOPE-B)	0.3	0.5	-$6,370,106	-$6,315,295
Bleed to Pettersson Score (≥ 25)	4.89	8.15	-$6,339,325	-$6,344,775
FIX joint bleeds (HOPE-B)	1.7625	2.9375	-$6,344,934	-$6,340,646
Etranadez all bleeds (HOPE-B)	1.1325	1.8875	-$6,342,700	-$6,340,124

Figure E4. Tornado Diagram on Incremental QALY for Etranacogene Dezaparvovec versus FIX

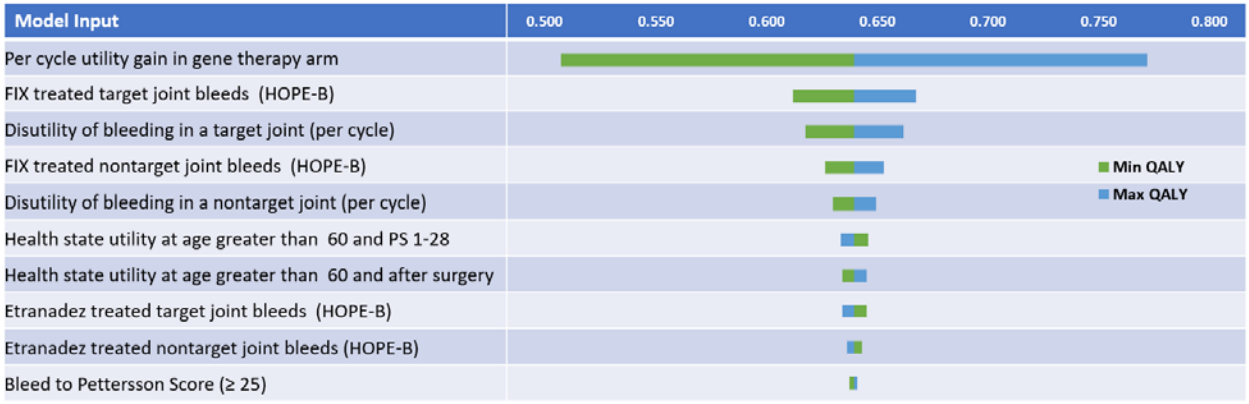


Table E19. Inputs and Results for Etranacogene Dezaparvovec versus FIX QALY Tornado Diagram

Inputs	Low Input Value	High Input Value	Min QALY	Max QALY
Per cycle utility gain in gene therapy arm	0.023	0.038	0.507	0.772
FIX treated target joint bleeds (HOPE-B)	1.598	2.663	0.612	0.667
Disutility of bleeding in a target joint (per cycle)	0.002	0.004	0.617	0.662
FIX treated nontarget joint bleeds (HOPE-B)	1.140	1.900	0.626	0.653
Disutility of bleeding in a nontarget joint (per cycle)	0.002	0.003	0.630	0.649
Health state utility at age greater than 60 and PS 1-28	0.405	0.675	0.645	0.633
Health state utility at age greater than 60 and after surgery	0.362	0.603	0.634	0.645
Etranadez treated target joint bleeds (HOPE-B)	0.330	0.550	0.645	0.634
Etranadez treated nontarget joint bleeds (HOPE-B)	0.300	0.500	0.643	0.636
Bleed to Pettersson Score (≥ 25)	4.890	8.150	0.636	0.641

Table E20 below summarizes the probabilistic sensitivity analyses. In 100 percent of the simulations etranacogene dezaparvovec was found to be cost effective even at very high willingness to pay thresholds.

Table E20. Probabilistic Sensitivity Analysis Cost per QALY Gained Results: Etranacogene Dezaparvovec Compared to Factor IX

	Cost Effective at $50,000 per QALY Gained	Cost Effective at $100,000 per QALY Gained	Cost Effective at $150,000 per QALY Gained	Cost Effective at $200,000 per QALY Gained
Etranacogene Dezaparvovec vs Factor IX	100%	100%	100%	100%

QALY: quality-adjusted life year

Model 2

Figures E5 and E6 and Tables E21 and E22 below show the tornado diagrams for model 2. Per cycle costs of emicizumab were found to have the largest impact on costs, but at all ranges of all the one way sensitivity analyses valoctocogene roxaparvovec was associated with lower costs. The fixed utility gain for valoctocogene roxaparvovec had the biggest impact on QALYs. However, at all ranges of all the variables in the one way, valoctocogene roxaparvovec was associated with higher QALYs.

Figure E5. Tornado Diagram on Incremental Cost for Valoctocogene Roxaparvovec versus Emicizumab

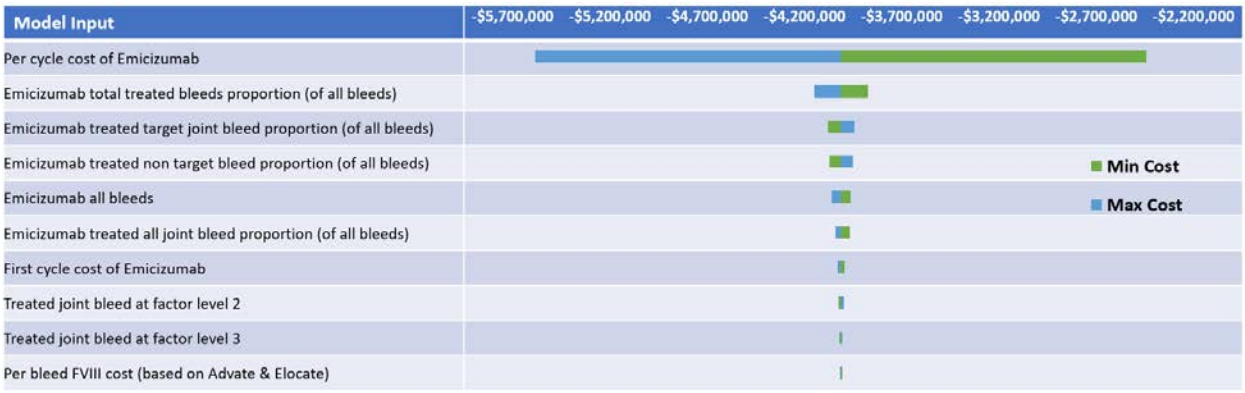


Table E21. Inputs and Results for Valoctocogene Roxaparvovec versus Emicizumab cost Tornado Diagram

Input	Low Input Value	High Input Value	Min Cost	Max Cost
Per cycle cost of Emicizumab	$220,557	$367,596	-$2,440,568	-$5,582,999
Emicizumab total treated bleeds proportion (of all bleeds)	0.38	0.63	-$3,874,318	-$4,149,249
Emicizumab treated target joint bleed proportion (of all bleeds)	0.20	0.34	-$4,080,484	-$3,943,083
Emicizumab treated non target bleed proportion (of all bleeds)	0.17	0.29	-$4,070,670	-$3,952,897
Emicizumab all bleeds	2.25	3.75	-$3,964,502	-$4,059,331
Emicizumab treated all joint bleed proportion (of all bleeds)	0.26	0.43	-$3,964,723	-$4,040,029
First cycle cost of Emicizumab	$254,489	$424,149	-$3,993,600	-$4,029,967
Treated joint bleed at factor level 2	1.89	3.15	-$4,026,311	-$3,997,280
Treated joint bleed at factor level 3	1.89	3.15	-$4,019,323	-$4,004,258
Per bleed FVIII cost (based on Advate & Elocate)	$5,440	$9,066	-$4,006,094	-$4,017,473

Figure E6. Tornado Diagram on Incremental QALY for Valoctocogene Roxaparvovec versus Emicizumab

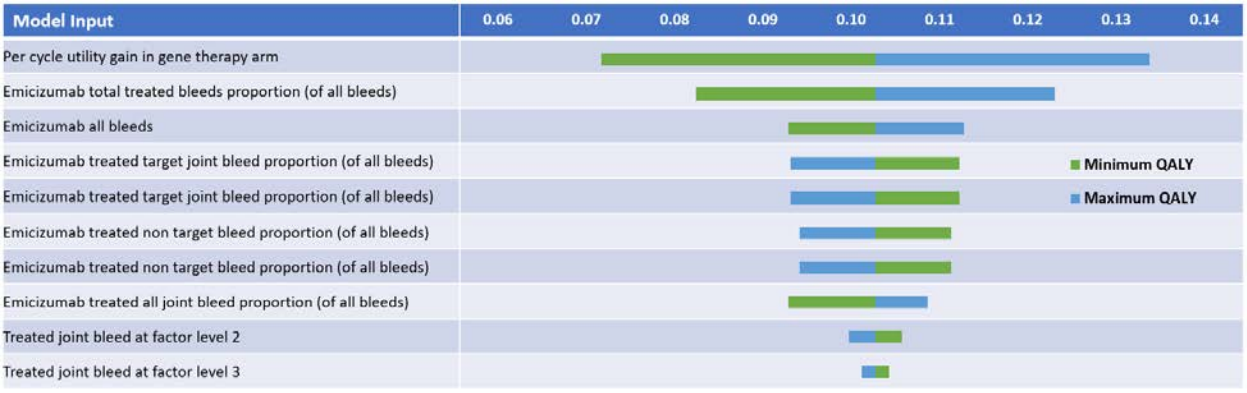


Table E22. Inputs and Results for Valoctocogene Roxaparvovec versus Emicizumab QALY Tornado Diagram

Input	Low Input Value	High Input Value	Minimum QALY	Maximum QALY
Per cycle utility gain in gene therapy arm	0.01	0.02	0.07	0.13
Emicizumab total treated bleeds proportion (of all bleeds)	0.38	0.63	0.08	0.12
Emicizumab all bleeds	2.25	3.75	0.09	0.11
Emicizumab treated target joint bleed proportion (of all bleeds)	0.20	0.34	0.11	0.09
Emicizumab treated target joint bleed proportion (of all bleeds)	0.20	0.34	0.11	0.09
Emicizumab treated non target bleed proportion (of all bleeds)	0.17	0.29	0.11	0.09
Emicizumab treated non target bleed proportion (of all bleeds)	0.17	0.29	0.11	0.09
Emicizumab treated all joint bleed proportion (of all bleeds)	0.26	0.43	0.09	0.11
Treated joint bleed at factor level 2	1.89	3.15	0.11	0.10
Treated joint bleed at factor level 3	1.89	3.15	0.10	0.10

Table E23 below summarizes the probabilistic sensitivity analyses. In 100 percent of the simulations valoctocogene roxaparvovec was found to be cost effective even at very high willingness to pay thresholds.

Table E23. Probabilistic Sensitivity Analysis Cost per QALY Gained Results: Valoctocogene Roxaparvovec versus Emicizumab

	Cost Effective at $50,000 per QALY Gained	Cost Effective at $100,000 per QALY Gained	Cost Effective at $150,000 per QALY Gained	Cost Effective at $200,000 per QALY Gained
Valoctocogene Roxaparvovec vs Emicizumab	100%	100%	100%	100%

QALY: quality-adjusted life year

E5. Scenario Analyses

We conducted the following scenario analyses in each model.

- Extending duration of disutility from bleeds to 7 full days from 2 full days and 5 half days.
- Doubling the bleed rates for patients with arthropathy across all treatments.
- A scenario where patients enter at the age of 40 and with a PS of 20.
- Scenarios in each version of the model where surgery returns patients to a PS of 20.
- A scenario with a relatively high AE cost of $2,200 included in cycle 1 in model 1 and in cycles 1 and 2 for model 2 based on estimates of potential costs provided by Genentech.
- Finally, a scenario where all patients switch treatment at a projected factor level of 5 IU/mL.

As both treatments meet ICERs Single or Short-Term Transformative (SST) framework, the following scenarios were also considered:

- 50/50 shared savings in which 50% of lifetime health care cost offsets from a new treatment are assigned to the health care system instead of being assigned entirely to the new treatment.

- Cost-offset cap in which health care cost offsets generated by a new treatment are capped at $150,000 per year but are otherwise assigned entirely to the new treatment.

In addition, we include a scenario with zero net savings assigned to the gene therapy.

Optimistic and conservative assumptions regarding the benefit of treatment, to be presented in conjunction with the full cost-offset analysis. *Note that the optimistic case for etranacogene dezaparvovec had efficacy with no decline across time and the pessimistic scenario used double the slope of the projected linear decline in factor levels. For Valoctocogene roxaparvovec the optimistic scenario used the same exponential decline in factor levels but capped projected bleeds at the 5% level. For the pessimistic scenario a linear projected decline in factor levels was used.*

We also conducted threshold analysis for duration of effect in patients receiving short-term benefit that would be needed to achieve cost-effectiveness thresholds.

Tables E24 and E25 show the non SST and the SST scenario results. All have etranacogene dezaparvovec as dominant at a price of $3,500,000 except the $150,000 per year cap and the zero shared savings scenarios where the cost per QALY for etranacogene dezaparvovec was very high.

Table E24. Non-SST Scenario Analysis Results (Model 1- Etranacogene Dezaparvovec vs FIX)

Scenario	Cost/QALY
Extending duration of disutility from bleeds to 7 full days from 2 full days and 5 half days.	Dominant
Doubling the bleed rates for patients with arthropathy across all treatments.	Dominant
A scenario where patients enter at the age of 40 and with a PS of 20.	Dominant
Scenario where surgery returns patients to PS of 20.	Dominant
Scenario where all patients switch at a factor level of 5 IU/mL.	Dominant
Scenario with high AE cost in cycle 1	Dominant

PS: Pettersson Score

Table E25. SST Scenario Analysis Results (Model 1- Etranacogene Dezaparvovec vs FIX)

Scenario	Cost/QALY
Shared savings in which 50% of lifetime health care cost offsets from etranacogene dezaparvovec are assigned to the health care system instead of being assigned entirely to etranacogene dezaparvovec.	Dominant
Cost-offset cap in which health care cost offsets generated by Etranacogene dezaparvovec are capped at $150,000 per year.	$997,000
Optimistic assumptions regarding the benefit of treatment, to be presented in conjunction with the full cost-offset analysis.	Dominant
Conservative assumptions regarding the benefit of treatment, to be presented in conjunction with the full cost-offset analysis.	Dominant
Zero net savings.	$5,121,000

Tables E26 and E27 show the scenario results in model 2. In each of the scenarios except the $150,000 cap in savings SST scenario and the zero shared savings scenario, valoctocogene roxaparvovec was found to be dominant using a placeholder price of $2,500,000. In the $150,000 cap and zero cost savings scenarios, however, valoctocogene roxaparvovec had a very high cost per QALY.

Table E26. Non-SST Scenario Analysis Results (Model 2- Valoctocogene Roxaparvovec vs Emicizumab)

Scenario	Cost/QALY
Extending duration of disutility from bleeds to 7 full days from 2 full days and 5 half days.	Dominant
Doubling the bleed rates for patients with arthropathy across all treatments.	Dominant
A scenario where patients enter at the age of 40 and with a PS of 20.	Dominant
Scenario where surgery returns patients to PS of 20	Dominant
Scenario where all patients switch at a factor level of 5 IU/mL.	Dominant
Scenario with high AE costs in cycles 1 and 2	Dominant

PS: Pettersson Score

Table E27. SST Scenario Analysis Results (Model 2- Valoctocogene Roxaparvovec vs Emicizumab)

Scenario	Cost/QALY
Shared savings in which 50% of lifetime health care cost offsets from valoctocogene roxaparvovec are assigned to the health care system instead of being assigned entirely to valoctocogene roxaparvovec.	Dominant
Cost-offset cap in which health care cost offsets generated by valoctocogene roxaparvovec are capped at $150,000 per year.	$5,354,000
Optimistic assumptions regarding the benefit of treatment, to be presented in conjunction with the full cost-offset analysis.	Dominant
Conservative assumptions regarding the benefit of treatment, to be presented in conjunction with the full cost-offset analysis.	Dominant
Zero net savings.	$21,060,000

Further Details for the Probabilisticy Sensitivity Analyses

Tables E28 and E29 below provide added details on the sensitivity analyses.

Table E28. Details on Model 1 Inputs for Sensitivity Analysis

Input	Lower Value	Upper Value	Distribution
Number of bleeds to increase Pettersson Score (age ≥ 25years)	4.89	8.15	Uniform
Number of bleeds to increase Pettersson Score (age < 25years)	27.39	45.65	Uniform
Factor IX all bleeds	3.14	5.24	Uniform
Factor IX joint bleed proportion (of all bleeds)	0.42	0.70	Uniform
Factor IX total treated bleeds proportion (of all bleeds)	0.65	1.09	Uniform
Factor IX treated all joint bleed proportion (of all bleeds)	0.45	0.75	Uniform
Factor IX treated target joint bleed proportion (of all bleeds)	0.38	0.64	Uniform
Factor IX treated non target bleed proportion (of all bleeds)	0.27	0.45	Uniform
Treated joint bleed at factor level 0	0.81	1.35	Uniform
Treated joint bleed at factor level 1	0.81	1.35	Uniform
Treated joint bleed at factor level 2	0.81	1.35	Uniform
Treated joint bleed at factor level 3	0.81	1.35	Uniform
Treated joint bleed at factor level 4	0.46	0.76	Uniform
Treated joint bleed at factor level 5	0.29	0.49	Uniform
Treated joint bleed at factor level 6	0.25	0.42	Uniform
Treated joint bleed at factor level 7	0.26	0.43	Uniform
Treated joint bleed at factor level 8	0.24	0.41	Uniform
Treated joint bleed at factor level 9	0.22	0.36	Uniform
Treated joint bleed at factor level 10	0.15	0.26	Uniform
Treated joint bleed at factor level 11	0.05	0.08	Uniform
Etranacogene dezaparvovec all bleeds (HOPE-B)	1.13	1.89	Uniform
Etranacogene dezaparvovec joint bleeds (HOPE-B)	0.38	0.64	Uniform
Etranacogene dezaparvovec treated nontarget joint bleeds (HOPE-B)	0.30	0.50	Uniform
Etranacogene dezaparvovec treated target joint bleeds (HOPE-B)	0.33	0.55	Uniform
FIX all bleeds (HOPE-B)	3.14	5.24	Uniform
FIX joint bleeds (HOPE-B)	1.76	2.94	Uniform

FIX treated nontarget joint bleeds (HOPE-B)	1.14	1.90	Uniform
FIX treated target joint bleeds (HOPE-B)	1.60	2.66	Uniform
Health state utility at age less than 30 and PS 0	0.71	1.00	Beta
Health state utility at age less than 30 and PS 1-27	0.62	1.00	Beta
Health state utility at age less than 30 and after surgery	0.54	0.89	Beta
Health state utility at age between 30 & 40 and PS 0	0.63	1.00	Beta
Health state utility at age between 30 & 40 and PS 1-28	0.56	0.93	Beta
Health state utility at age between 30 & 40 and after surgery	0.49	0.81	Beta
Health state utility at age between 40 & 50 and PS 0	0.65	1.00	Beta
Health state utility at age between 40 & 50 and PS 1-28	0.52	0.86	Beta
Health state utility at age between 40 & 50 and after surgery	0.46	0.76	Beta
Health state utility at age between 50 & 60 and PS 0	0.62	1.00	Beta
Health state utility at age between 50 & 60 and PS 1-28	0.47	0.79	Beta
Health state utility at age between 50 & 60 and after surgery	0.42	0.70	Beta
Health state utility at age greater than 60 and PS 0	0.55	0.91	Beta
Health state utility at age greater than 60 and PS 1-28	0.41	0.68	Beta
Health state utility at age greater than 60 and after surgery	0.36	0.60	Beta
Per cycle utility gain in gene therapy arm	0.02	0.04	Beta
Disutility of bleeding in a nontarget joint (per cycle)	0.00	0.00	Beta
Disutility of bleeding in a target joint (per cycle)	0.00	0.00	Beta
Cost of Etranacogene dezaparvovec	$3,000,000	$5,000,000	Gamma
Per year cost of Factor IX	$177,312	$295,520	Gamma
Per bleed Factor IX cost	$8,177	$13,629	Gamma
Per bleed non-drug cost (age 18-45years)	$3,624	$6,040	Gamma
Per bleed non-drug cost (age 45+ years)	$5,398	$8,997	Gamma
Per cycle arthropathy cost (PS14-28)	$487	$811	Gamma
Cost of surgery	$35,199	$58,665	Gamma
Societal cost per bleed	$926	$1,544	Gamma

Table E29. Details on Model 2 Inputs for Sensitivity Analysis

Input	Lower Value	Upper Value	Distribution
Number of bleeds to increase Pettersson Score (≥ 25)	4.89	8.15	Uniform
Number of bleeds to increase Pettersson Score (< 25)	27.39	45.65	Uniform
Emicizumab all bleeds	2.25	3.75	Uniform
Emicizumab joint bleed proportion (of all bleeds)	0.50	0.83	Uniform
Emicizumab total treated bleeds proportion (of all bleeds)	0.38	0.63	Uniform
Emicizumab treated all joint bleed proportion (of all bleeds)	0.26	0.43	Uniform
Emicizumab treated target joint bleed proportion (of all bleeds)	0.20	0.34	Uniform
Emicizumab treated non target bleed proportion (of all bleeds)	0.17	0.29	Uniform
Treated joint bleed at factor level 0	1.89	3.15	Uniform
Treated joint bleed at factor level 1	1.89	3.15	Uniform
Treated joint bleed at factor level 2	1.89	3.15	Uniform
Treated joint bleed at factor level 3	1.89	3.15	Uniform
Treated joint bleed at factor level 4	1.07	1.78	Uniform
Treated joint bleed at factor level 5	0.68	1.14	Uniform
Treated joint bleed at factor level 6	0.59	0.98	Uniform
Treated joint bleed at factor level 7	0.60	1.00	Uniform
Treated joint bleed at factor level 8	0.57	0.95	Uniform

Treated joint bleed at factor level 9	0.50	0.84	Uniform
Treated joint bleed at factor level 10	0.36	0.60	Uniform
Treated joint bleed at factor level 11	0.12	0.20	Uniform
Total bleed rate (cycle 0 - GENEr8-1 trial)	0.69	0.99	Uniform
Total bleed rate (cycle 1 - GENEr8-1 trial)	0.53	0.71	Uniform
Total bleed rate (cycle 2 - GENEr8-1 trial)	0.46	0.60	Uniform
Total bleed rate (cycle 3 - GENEr8-1 trial)	0.40	0.53	Uniform
Total bleed rate (cycle 4 - GENEr8-1 trial)	0.35	0.46	Uniform
Total bleed rate (cycle 5 - GENEr8-1 trial)	0.30	0.40	Uniform
Total bleed rate (cycle 6 - GENEr8-1 trial)	0.26	0.35	Uniform
Total bleed rate (cycle 7 - GENEr8-1 trial)	0.24	0.31	Uniform
Total bleed rate (cycle 8 - GENEr8-1 trial)	0.21	0.28	Uniform
Health state utility at age less than 30 and PS 0	0.71	1.00	Beta
Health state utility at age less than 30 and PS 1-27	0.62	1.00	Beta
Health state utility at age less than 30 and after surgery	0.54	0.89	Beta
Health state utility at age between 30 & 40 and PS 0	0.63	1.00	Beta
Health state utility at age between 30 & 40 and PS 1-28	0.56	0.93	Beta
Health state utility at age between 30 & 40 and after surgery	0.49	0.81	Beta
Health state utility at age between 40 & 50 and PS 0	0.65	1.00	Beta
Health state utility at age between 40 & 50 and PS 1-28	0.52	0.86	Beta
Health state utility at age between 40 & 50 and after surgery	0.46	0.76	Beta
Health state utility at age between 50 & 60 and PS 0	0.62	1.00	Beta
Health state utility at age between 50 & 60 and PS 1-28	0.47	0.79	Beta
Health state utility at age between 50 & 60 and after surgery	0.42	0.70	Beta
Health state utility at age greater than 60 and PS 0	0.55	0.91	Beta
Health state utility at age greater than 60 and PS 1-28	0.41	0.68	Beta
Health state utility at age greater than 60 and after surgery	0.36	0.60	Beta
Per cycle utility gain in gene therapy arm		0.02	Beta
Disutility of bleeding in a nontarget joint (per cycle)	0.002	0.003	Beta
Disutility of bleeding in a target joint (per cycle)	0.003	0.004	Beta
Cost of Valoctocogene Roxaparvovec	$1,875,000	$3,125,000	Gamma
First cycle cost of Emicizumab	$254,489	$424,149	Gamma
Per cycle cost of Emicizumab	$220,557	$367,59	Gamma
Per bleed FVIII cost (based on Advate & Eloctate)	$5,439	$9,066	Gamma
Per bleed non-drug cost (18-45years)	$3,624	$6,040	Gamma
Per bleed non-drug cost (45+ years)	$5,398	$8,997	Gamma
Per cycle arthropathy cost (PS14-28)	$486	$811	Gamma
Cost of surgery	$35,198	$58,665	Gamma
Societal cost per bleed	$926	$1,544	Gamma
Adverse effect cost (prednisolone)	$9	$14	Gamma

E6. Threshold Analyses

As discussed in the Report, an aspect of the decision to use a shared savings model as the basis of Health Benefit Price Benchmarks (HBPBs) is the percentage of a traditionally calculated HBPB that comes from cost offsets. This calculation is 1 – (150,000*incremental QALYs/150,000 threshold price). For etranacogene dezaparvovec, this is 100*[1-(150,000*0.64/9,939,000)] or 99%. For valoctocogene roxaparvovec, this is 100*[1-(150,000*0.10)/6,723,000) or 99.8%.

E7. Heterogeneity and Subgroups

There was not enough evidence to support heterogeneity or subgroup analyses of the gene therapies.

E8. Model Validation

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

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

Prior Economic Models

Model 1

Very few cost effectiveness related models exist for hemophilia B. Past models that project costs for hemophilia B have a similar finding as here that costs are largely driven by the cost of treatment with factor IX.

Model 2

Details of models for patients with hemophilia A with inhibitors can be found in a 2018 ICER report. Additionally, details on prior economic analyses for hemophilia A patients with inihibitors can be found in the 2020 ICER report on hemophilia A. The updated model in hemophilia A includes a different projection method for projecting factor levels as well as updated data. The updated model also adds a data driven utility gain associated with gene therapy. The same basic differences between the updated model and prior models in the literature otherwise were the same as discussed in the prior report.

F. Potential Budget Impact: Supplemental Information

Methods

To estimate the size of the potential candidate population for treatment in PBIA 1, we use inputs for total projected US population (~342,000,000)[74] and proportion male (49.5%),[75] and a Centers for Disease Control (CDC) epidemiological study for estimates of age-adjusted prevalence of hemophilia B (.0037%),[76] proportion of hemophilia B cases occurring in adults (52.8%),[76] and proportion with severe disease (28.7%).[76] While published estimates of the proportion of severe hemophilia B patients without inhibitors are of generally low quality, one recent global study in severe patients <18 years estimates 90.9% of these patients do not have inhibitors.[77] Taken together, applying these sources results in an estimate of approximately 860 eligible patients in the US for PBIA 1. For the purposes of this analysis, we assume that 20% of these patients in PBIA 1 would initiate treatment in each of the five years, or approximately 172 patients per year.

While we ultimately do not report findings for PBIA 2, we did make attempts to estimate the corresponding population size of US adult patients with severe Hemophilia A without inhibitors. To estimate the size of the potential candidate population for treatment in PBIA 2, we used inputs for total projected US population over 2022-2026 (~342,000,000)[74], proportion male (49.5%),[75] age-adjusted prevalence of hemophilia A from a Centers for Disease Control (CDC) epidemiological study of individuals visiting hemophilia treatment centers (.012%),[76] proportion of hemophilia A cases occurring in adults (52.8%)[76] and proportion with severe disease (defined as baseline factor activity level <1%) (48.2%)[76] from the same CDC study, and an estimate of the percentage of severe hemophilia A patients who do not have inhibitors (87.2%).[78] Valoctocogene roxaparvovec trials also included a portion of those individuals eligible for prophylaxis without severe disease. To account for these individuals, we apply an 11% increase to the calculated number of severe patients. Applying these sources results in an estimate of approximately 5,010 eligible patients in the US. For the purposes of this analysis, we will assume that 20% of these patients in PBIA 2 would initiate treatment in each of the five years, or approximately 1,002 patients per year.

Results

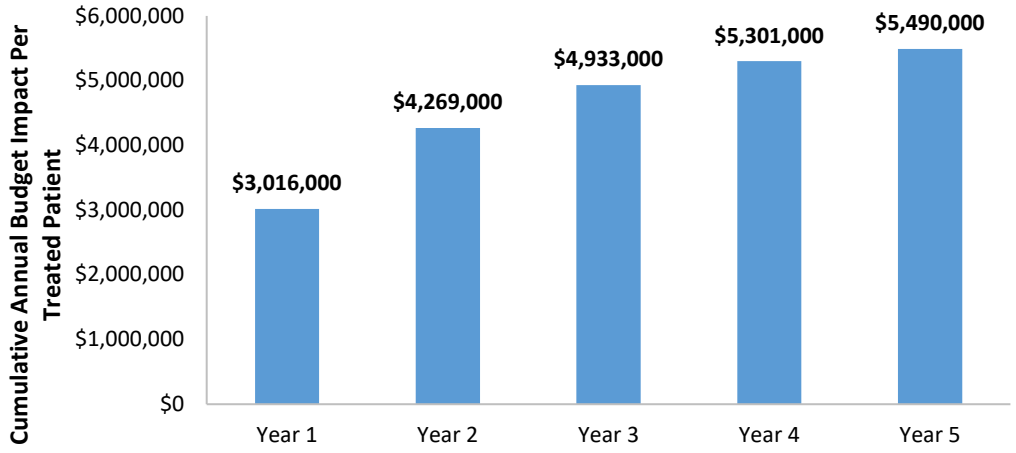
Table F1 describes the per-patient budget impact calculations for etranacogene dezaparvovec at its price ($3.5 million per year), and the prices to reach $150,000, $100,000, and $50,000 per QALY ($2.958 million, $2.926 million, and $2.894 million per year, respectively) compared factor IX therapy. Similarly, Figure F1 visualizes etranacogene dezaparvovec's cumulative net budget impact per treated patient per year at its price, assuming an incremental 20% uptake per year.

Table F1. Per-Patient Budget Impact Calculations Over a Five-Year Time Horizon

	Average Annual Per Patient Budget Impact			
	Price	**$150,000/QALY**	**$100,000/QALY**	**$50,000/QALY**
Etranacogene dezaparvovec compared to factor IX therapy	$1,098,000	$850,000	$836,000	$821,000

QALY: quality-adjusted life year, WAC: wholesale acquisition cost

Figure F1. Cumulative Per-Patient Budget Impact Calculations Over a Five-Year Time Horizon at Etranacogene Dezaparvovec Price



G. Supplemental Policy Recommendations

Coverage Criteria: General

ICER has previously described general criteria for fair coverage policies that should be considered as cornerstones of any drug coverage policy: https://icer.org/wpcontent/uploads/2020/11/Cornerstones-of-Fair-Drug-Coverage-_-September-28-2020.pdf

Drug-specific Coverage Criteria

Coverage Criteria Considerations for Etranacogene dezaparvovec for Hemophilia B

Patient Eligibility Criteria

a. **Diagnosis**: Hemophilia B is often diagnosed in infancy based on testing performed at birth if there is a maternal family history or if there is clinical concern raised by bleeding. Repeated testing to confirm eligibility is not necessary.
b. **Clinical eligibility**: Patients eligible for gene therapy will likely be all patients with "severe phenotype" hemophilia B (nearly all patients with "severe" hemophilia B as defined by a factor activity level <1%) and some patients with "moderate" hemophilia B as defined by a factor activity level between 1% and 5%. Clinical experts argue that phenotype is the most important way to determine when patients with factor activity level between 1% and 5% require factor IX prophylaxis, but some payers may wish to establish a specific factor level (e.g. 2%) below which all patients qualify for coverage, whereas patients with higher factor level will require some history of use of prophylaxis based on bleeding history. Because of the limited evidence base, it is highly likely that payers will limit coverage to patients matching the inclusion criteria of the phase 3 clinical trial: males ≥ 18 years of age currently on a stable dose of factor IX prophylaxis with at least 150 exposure days of prophylaxis with factor IX.
c. **Exclusions**: Clinical experts and patient representatives have argued for many years that payers should not exclude patients who have never bled from receiving prophylaxis and should not require a specific number or location of bleeds for coverage of prophylaxis or gene therapy. Exclusion criteria from the pivotal clinical trial include the presence of factor IX inhibitors, uncontrolled HIV, and active hepatitis B or C infection.

Step Therapy

There are no other treatments other than factor prophylaxis and therefore the potential for step therapy is not applicable.

Provider Qualification Restrictions

a. **Payers should require that the delivery of gene therapy with *etranacogene dezaparvovec* be done by or in consultation with a Hemophilia Treatment Center (HTC).** Gene therapy is in its infancy and patients may only get one chance to be treated, at least with an AAV-vector delivery system. In addition, the initial monitoring and management are unique and are best delivered by experienced centers. Payers should be vigilant to ensure that patients who live far from an HTC have adequate coverage of travel or other necessities required to be able to access care.

Duration of coverage and renewal criteria:
Not applicable as this is a one-time therapy.

Coverage Criteria Considerations for Valoctocogene roxaparvovec for Hemophilia A.

Patient Eligibility Criteria

a. **Diagnosis**: Hemophilia A is often diagnosed in infancy based on testing performed at birth if there is a maternal family history or if there is clinical concern raised by bleeding. Repeated testing to confirm eligibility is not necessary.
b. **Clinical eligibility:** If approved by the FDA, patients eligible for gene therapy will likely include all patients with "severe" hemophilia A. One way to define severe hemophilia A is reflected in the phase 3 clinical trial eligibility criteria: patients with factor activity level <1%. Because of the limited evidence base and high cost, payers are likely to limit coverage to patients matching this and other inclusion criteria of the phase 3 clinical trial, but payers should expand coverage criteria to include patients currently on emicizumab prophylaxis: males ≥ 18 years of age currently on a stable dose of factor VIII or emicizumab prophylaxis for ≥12 months and with at least 150 exposure days of prophylaxis with factor VIII if that is the chosen prophylactic therapy.
c. Payers should also consider whether to include coverage provisions for some patients with factor activity level between 1% and 5%. Clinical experts argue that phenotype is the most important way to determine when patients with factor activity level between 1% and 5% require factor VIII prophylaxis, and therefore payers should consider providing coverage for patients with factor levels between 1% and 5% if they are on routine prophylaxis due to a history of significant bleeds.
d. **Exclusions**: Clinical experts and patient representatives have argued for many years that payers should not exclude patients who have never bled from receiving prophylaxis and should not require a specific number or location of bleeds for coverage of prophylaxis or gene therapy. Exclusion criteria from the pivotal clinical trial include the presence of factor VIII inhibitors, uncontrolled HIV, and active hepatitis B or C infection.

Step Therapy

At least one national payer has suggested to patient representatives that step therapy with emicizumab is being considered prior to provision of coverage for Valrox. Clinical experts and patient experts view this approach as lacking any clinical justification and appears to be only a method for trying to avoid the high one-time fee for gene therapy while assuming that patients may switch insurers before the cost-saving potential of gene therapy is fully realized. In short, step therapy does not appear to be a reasonable consideration for this treatment.

Provider Qualification Restrictions

a. **Payers should require that the delivery of gene therapy with *valoctocogene roxaparvovec* be done by or in consultation with a Hemophilia Treatment Center (HTC).** Gene therapy is in its infancy and patients may only get one chance to be treated, at least with an AAV-vector delivery system. In addition, the initial monitoring and management are unique and are best delivered by experienced centers. Payers should be vigilant to ensure that patients who live far from an HTC have adequate coverage of travel or other necessities required to be able to access care.

Duration of coverage and renewal criteria:
Not applicable as this is a one-time therapy.

H. Public Comments

This section includes summaries of the public comments prepared for the CTAF Public Meeting on Friday, November 18, 2022. These summaries were prepared by those who delivered the public comments at the meeting and are presented in order of delivery. Three speakers did not submit summaries of their public comments.

A video recording of all comments can be found here.

Debbie Bensen-Kennedy, MD, CSL Behring
Vice President, Medical Affairs

CSL Behring appreciates ICER's assessment of etranacogene dezaparvovec, or for brevity EtranaDez, in recognizing its value as an innovative gene therapy for people with hemophilia B. ICER's clinical evaluation has concluded there is an incremental to substantial health benefit of EtranaDez, with moderate certainty, in comparison to factor IX (FIX) prophylaxis. Further, ICER's economic evaluation of EtranaDez compared with FIX prophylaxis revealed that EtranaDez was a dominant treatment with lower cost and higher QALYs at the model placeholder price of $4 million dollars. ICER consistently found cost-effectiveness at a cost of up to $9.97M for EtranaDez in the base case analysis, highlighting the substantial economic value that EtranaDez can bring to the health system, in addition to its clinical benefit. We appreciate this opportunity to comment on ICER's evaluation.

In this ICER assessment, EtranaDez demonstrated its transformational impact for both people with hemophilia B and the health system. From the patients' perspective, ICER acknowledged that treatment with EtranaDez resulted in a significant reduction in annualized bleeding rates (ABRs), ranging between 64% for all bleeds to 80% for treated joint bleeds, as reported from the Phase 3 HOPE-B trial,1 in addition to alleviating the pain and minimizing potential disability from bleeding events. Further, the reduction in burden of therapy from weekly or more frequent intravenous FIX injection was highlighted as an important benefit, with 96% of the participants in the HOPE-B trial1 discontinuing FIX prophylaxis. Of note, 100% of the 52 patients with successful transduction were free from continuous FIX prophylaxis.

CSL Behring appreciates that ICER recognized the clinical benefit and cost effectiveness of EtranaDez compared with FIX prophylaxis. We do, however, have a few comments we would like you to consider.

From the economic and health system perspective, CSL Behring is in alignment with ICER in regard to the key components in the economic evaluation of EtranaDez and appreciate the demonstration of cost-effectiveness in various scenario analyses. However, while we respect ICER's approach on single and short-term therapies (SST) resulting in a large cost-offset, our perspective is that using an

arbitrary number of $150,000 as a cost-offset cap to derive the health benefit price benchmarks (HBPB) for EtranaDez does not accurately reflect the value of the treatment options for hemophilia B.

People with Hemophilia B who would be eligible for gene therapy have a severe clinical phenotype. While the current standard of care (SOC) for these patients, FIX prophylaxis, can cost between $565K and $753K annually, it is a life-saving treatment that has lengthened life expectancy for people with severe hemophilia B by 5-fold.6; 7 In the absence of alternative treatment options, the assumption of one QALY gain is inappropriate given the drastic reduction in lifespan that would be expected if a person with hemophilia B were to discontinue FIX prophylaxis.

It appears, in the process of highlighting the cost-offset cap analysis, that an edit was made renaming the base case to "full cost-offset." ICER has used “base case” consistently throughout its history and without supplying context, this term “full cost-offset” is highly likely to be misinterpreted. We politely request ICER to revert the wording to base case analysis for consistency with all previous ICER assessments. We would also request the order of analyses in the results table be consistent with prior reporting.

Finally, in ICER’s budget impact analysis, we are in agreement with the assumption relating to the gene therapy eligible population. However, we believe the assumption of an annual uptake of 20% of eligible patients dosed with EtranaDez is unrealistic. This logic would assume all severe patients will receive EtranaDez within 5 years. These assumptions lead to an overestimation of the budget impact of EtranaDez. Furthermore, we would like to point out that the 5-year time horizon substantially underestimates the value of EtranaDez. By year 6 all costs from EtranaDez would be offset. In subsequent years EtranaDez would be highly cost saving to the health system. We feel that adding comments in the report regarding the longer-term cost saving potential of EtranaDez is justified.

CSL Behring is proud to be bringing people with hemophilia B a novel therapy with greater clinical and economic value than the current standard of care. We commend ICER for a thorough and reasonable assessment, although at the same time ask that our comments be considered in the final version of the report. In closing, we thank the hemophilia B community for their continued collaboration and support. We will continue to work with stakeholders to ensure that both patients and the health system can benefit from EtranaDez.

Wing Yen Wong, MD, BioMarin Pharmaceuticals, Inc.
Special Advisor, Worldwide Research & Development (WWRD)

On behalf of BioMarin, I appreciate the opportunity to provide comments on the ICER's Evidence Report "Gene Therapy for Hemophilia B and an Update on Gene Therapy for Hemophilia A: Effectiveness and Value".1

Severe hemophilia A is associated with spontaneous bleeding and painful, disabling arthropathies.2-4 Prophylaxis with Factor VIII (FVIII) or emicizumab requires routine administrations of 100-150 infusions or 12 to 52 injections per year, respectively,5-7 costing well over $600,000 annually.8 In a large, prospective, non-interventional study of individuals with severe hemophilia A receiving regular prophylaxis with FVIII, more than 75% of participants reported bleeding episodes, with a mean annualized bleeding rate (ABR) of 5, despite over 90% adherence with their prescribed FVIII regimen.6 Other studies indicate that suboptimal adherence persists over time, further compromising outcomes.9-11

The Phase 3 clinical trial, GENEr8-1, demonstrated that gene transfer with valoctocogene roxaparvovec provides superior bleed protection relative to repeated exogenous FVIII prophylaxis: a single infusion in adult men with severe hemophilia A previously receiving FVIII prophylaxis resulted in a >80% reduction in the number of treated bleeds requiring treatment each year and a 98% reduction in the use of FVIII.12,13 It is worth noting that, during 2 to 3 years of follow-up to date, 74% of participants had no bleeds requiring treatment and >95% remained free from prophylaxis.12,13 In addition, participants demonstrated broad and consistent improvements in health-related quality of life sustained through 2 years post gene transfer.14 Measured on the Hemophilia-specific Quality of Life Questionnaire for Adults, clinically meaningful improvements were reported in domains of 'role functioning', 'consequences of bleeding', 'worry', and 'treatment concern'. Participants also reported less classroom and work impairment after gene transfer compared with baseline levels. Measures of functional abilities showed improvements in all domains over 2 years, with the largest effects seen in leisure activities and sports, demonstrating improved physical activity and strength.14

Valoctocogene roxaparvovec has demonstrated an acceptable, well tolerated safety profile in the clinical development program to date. Transient, asymptomatic, grade 1-3 transaminitis, and transient infusion reactions were the most common side effects.15,16 Patients with transaminitis were responsive to temporary immunosuppression, and showed no symptoms or sequelae suggestive of clinically significant hepatocellular injury or liver dysfunction.15,16

In its report, ICER raises concerns about the high rate and prolonged use of corticosteroids in the clinical trials. Corticosteroid treatment in GENEr8-1 was initiated at the investigator's discretion and it is acknowledged that a propensity for corticosteroid use was observed.16 Analysis of

corticosteroid usage and FVIII and ABR outcomes support lesser use of corticosteroids, and we expect that immunosuppression with corticosteroids will be less intensive in the post-approval setting than was observed in the clinical trials. The European label for valoctocogene roxaparvovec reflects a more restrained use of corticosteroids.17 BioMarin will monitor the use of immunosuppressant regimens in the real world with comprehensive follow-up of valoctocogene roxaparvovec recipients through 15 years, as well as conducting a post-approval registry study.

While BioMarin appreciates ICER's recognition of the long-term value of valoctocogene roxaparvovec, we respectfully disagree with ICER's approach of applying a $150,000 per year cap in costs offset by the treatment to set the price for valoctocogene roxaparvovec. BioMarin recognizes the financial burden of current hemophilia treatments and understands the rationale for applying a shared savings scenario analysis as part of ICER's 'high-impact single and short-term therapy (SST)' framework. However, these are arbitrary thresholds on which to set price recommendations. The applied annual cap of $150,000 cost saving is far below the real-world annual cost of prophylaxis, which exceeds $600,000 per patient in the United States.8

The outcomes-based warranty agreement that BioMarin plans to offer for valoctocogene roxaparvovec is designed to address variability and durability concerns for payers and health systems. It also reflects BioMarin's belief in the clinical value of valoctocogene roxaparvovec and our willingness to stand behind the value proposition and compensate payers and health systems in rare cases of sub-optimal responses during the warranty period.

Following the approval of valoctocogene roxaparvovec in Europe, a clinical trial participant* shared his personal perspective: "*the impact of gene therapy on my day to day, it has been a life change, it has been a big change…try a little of what I have never had. The peace of mind of living day to day, without being afraid of everything. That's the 3 years that I've had so far. A normal life.*"

Thank you very much; we appreciate the ongoing engagement between BioMarin and ICER and we look forward to continuing to work together to improve the lives of people with hemophilia.

I. Conflict of Interest Disclosures

Tables H1 through H3 contain conflict of interest (COI) disclosures for all participants at the Friday, November 18, 2022 CTAF Public Meeting.

Table H1. ICER Staff and Consultants and COI Disclosures

ICER Staff and Consultants	
Belen Herce-Hagiwara, BA,* Research Assistant, ICER	**David Rind, MD, MSc**,* Chief Medical Officer, ICER
Yasmine Kayali, BA,* Program Coordinator, ICER	**Liis Shea, MA,*** Program Director, ICER
Shahariar Mohammed Fahim, PhD,* Research Lead, Evidence Synthesis, ICER	**Jeff Tice, MD,*** Professor of Medicine, ICER
Ashton Moradi, PharmD, MS,* Health Economist, ICER	**Surrey Walton, PhD**,* Professor, College of Pharmacy-Pharmacy Systems Outcomes and Policy, UIC

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

Table H2. CTAF Panel Member Participants and COI Disclosures

Participating Members of CTAF	
Ralph G. Brindis, MD, MPH* Clinical Professor of Medicine, UCSF	**Jeffrey Klingman, MD*** Chair of Neurology, Kaiser Permanente Northern California
Felicia Cohn, PhD* Bioethics Director, Kaiser Permanente Orange County	**Joy Melnikow, MD, MPH*** Professor emeritus, UC Davis
Robert Collyar* Patient Advocates in Research (PAIR)	**Ann Raldow, MD, MPH*** Assistant Professor, Department of Radiation Oncology at UCLA
Sanket Dhruva, MD, MHS* Assistant Professor of Medicine, UCSF	**Rita F. Redberg, MD, MSc*** Professor of Medicine, UCSF
Rena K. Fox, MD* Professor of Medicine, UCSF	**Richard Seiden, JD*** Patient Advocate, Retired Partner, Foley & Lardner LLP
Kimberly Gregory, MD, MPH* Vice Chair OB GYN Cedars-Sinai	**Anthony Sowry, BA*** Patient Advocate and Lead Volunteer, National Patient Advocate Foundation
Paul Heidenreich, MD* Professor Medicine, Stanford University	

*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.

Table H3. Policy Roundtable Participants and COI Disclosures

Policy Roundtable Participant	Conflict of Interest
Debbie Bensen-Kennedy, MD, CSL Behring	Dr. Bensen-Kennedy is a full-time employee of CSL Behring.
Chuck Bucklar, BS, BioMarin	Mr. Bucklar is a full-time employee of BioMarin.
Miguel A. Escobar, MD, McGovern School of Medicine	Dr. Escobar has received honoraria from NovoNordisk, CSL Behring, Genentech, Biomarin, Sanofi, Takeda, Pfizer, NHF, Bayer, Hemabiologics/LFB, UniQure, Magellan.
Leslie Fish, PharmD, IPD Analytics	Dr. Fish is a full-time employee of IPD Analytics.
Brian O'Mahony, FACSLM, Irish Hemophilia Society	Mr. O'Mahony has received consulting fees or honoraria from Bayer Healthcare and BioMarin.
Margaret Ragni, MD, MPH, University of Pittsburgh Medical Center, Hemophilia Center of Western PA	Dr. Ragni is a member of BioMarin Advisory Board; Consultant, Advisory Board member and Symposium Speaker for Takeda. Her university also receives funding from Biomarin and SPARK.
Michael Sherman, MD, MBA, MS, Point32Health	Dr. Sherman is a full-time employee of Point32Health.
Mark Skinner, JD, Institute for Policy Advancement Ltd.	Mr. Skinner has received honoraria from F. Hoffman-La Roche / Genentech, Bayer Healthcare, BioMarin, Novo Nordisk and the Blue Cross Blue Shield Association.