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

Draft Evidence Report

September 13, 2022

Prepared for

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Jefferey 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, Liis Shea, and Janet Chu for their contributions to this Report.

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In the development of this report, ICER's researchers consulted with several clinical experts, patients, manufacturers, and other stakeholders. The following experts provided input that helped guide the ICER team as we shaped our scope and report. It is possible that expert reviewers may not have had the opportunity to review all portions of this draft 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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Novartis, and Regeneron. These holdings are independently managed by a financial advisor with instructions not to invest in companies with a known interest in therapies for bleeding disorders. Mr. Skinner is a member of the ICER Governing Board; Board of Directors of the World Federation of Hemophilia USA, which receives product and monetary donations for a global humanitarian aid program; serves as a consultant for the US National Hemophilia Foundation, and is a member of the NHF Scientific Advisory Council. Mr. Skinner is a Principal investigator for the Patient-Reported Outcomes and Burdens and Experiences (PROBE) study, which has received fees and grant support from Bayer, BioMarin, CSL-Behring, Freeline Therapeutics, Novo Nordisk, F. Hoffman-La Roche, Sanofi, Sobi, Takeda, uniQure. The PROBE study is an independent, investigator-led research project led by patients and patient advocacy organizations. Mr. Skinner is a person with severe hemophilia A.

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List of Acronyms and Abbreviations Used in this Report

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

Executive Summary

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.[3,4] 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 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 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 again 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. We found that both etranacogene dezaparvovec and valoctocogene roxaparvovec were dominant treatments at placeholder prices of $2,500,000 with substantial cost savings along with projected gains in quality adjusted life years. These findings were robust to numerous sensitivity analyses and scenario analyses.

The only exception was when savings from cost offsets were capped at $150,000 per year and the rest returned to society rather than the manufacturer. In this scenario, valoctocogene roxaparvovec was not cost effective.

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.[3,4] 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.

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 accepted CSL Behring's biologic license application for etranacogene dezaparvovec for priority review on May 24, 2022 with an expected FDA decision in late 2022 or early 2023. Valoctogene roxaparvovec was approved for the treatment of severe hemophilia A adults on August 24, 2022 by the European Commission.

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.

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[13,14] 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[21-26] 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] Presumably, the majority of these continued factor prophylaxis, though the details are not reported. 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 was 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 Eculizumab 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 median 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]

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 less rapid, 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

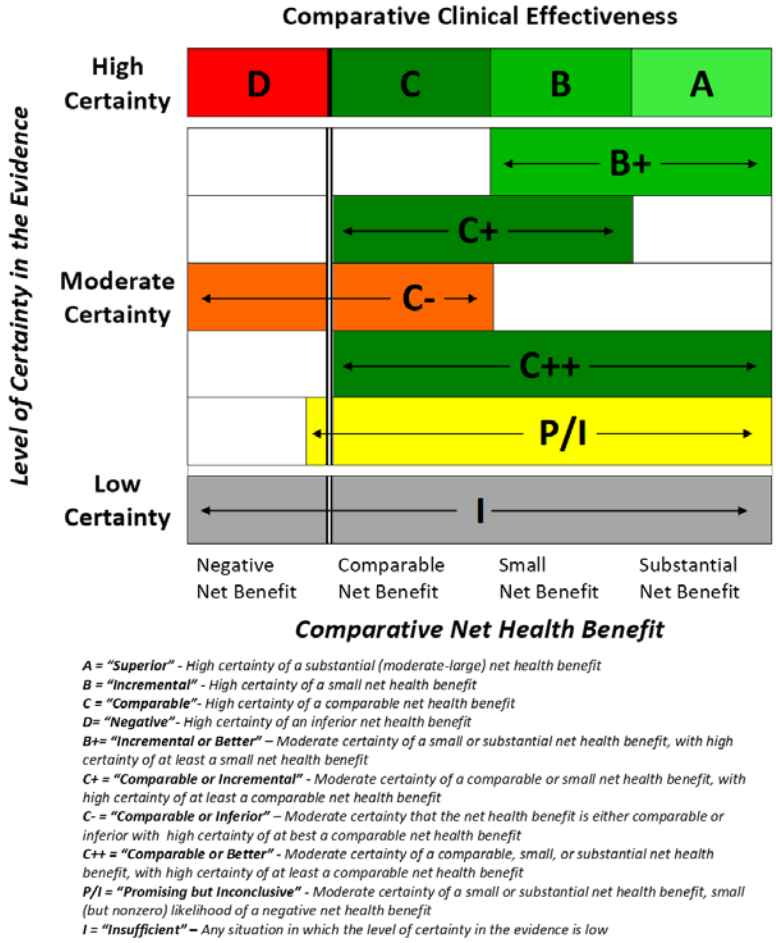
There are similar concerns about the evidence base for valoctocogene roxaparvovec as there were when ICER last reviewed the therapy. As with etranacogene dezaparvovec, the trials use a single arm design and are relatively small, particularly when looking at follow-up beyond two years. The data from the 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



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++

4. Long-Term Cost Effectiveness

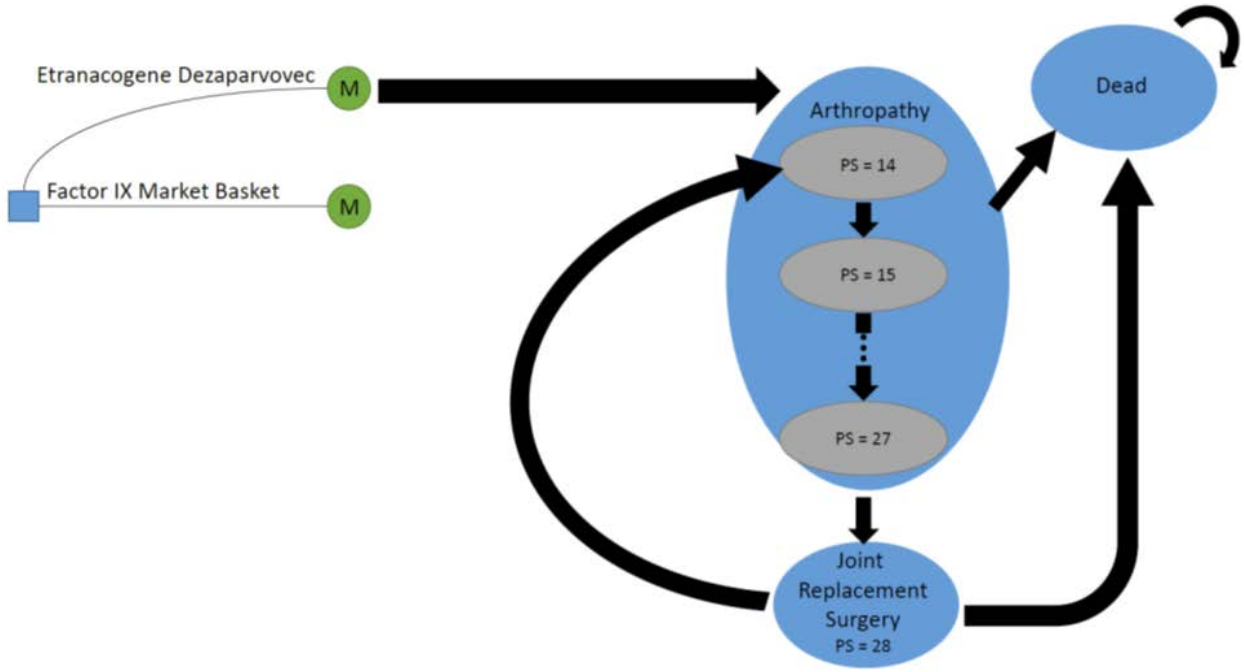
4.1. Methods Overview

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 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 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 base case 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.

Figure 4.1. Model Schematic



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.[32-36] 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.[37,38]

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 were taken from the HOPE trial.[9] 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.

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 a rebate and literature-based estimates of bleed rates across factor levels.[17,39] 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.[22,40]
- 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.[41]

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.[42] 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).[43] 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.[32-34,44] 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 [33,44]

Drug Costs

Model 1

See Table E11 for details on dosing. As etranacogene dezaparvovec has not been approved, no WAC or net price estimates are available. We therefore conducted the base-case analysis using a placeholder price of $2,500,000 which is a midpoint of suggested ranges of gene therapy seen online for hemophilia A (see Table 4.1 below). In the absence of data on usual discounts for gene therapy, we assumed no discounting and used this price as the net price. 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	$2,500,000	N/A	$2,500,000
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

*Placeholder prices for etranacogene dezaparvovec and 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.

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 will conduct the base-case analysis using a placeholder price of $2,500,000, based on statements from the manufacturer indicating consideration of prices of around $2 million to $3 million per treatment.[45] 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. 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	$2,500,000
Emicizumab	$25,706	12%‡	$639,543†

*Placeholder price for valoctocogene roxaparvovec and 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

Base-Case Results

Model 1

Table 4.3 below shows the base-case results for model 1 using a placeholder price for etranacogene dezaparvovec of $2,500,000. 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 Base-Case for Etranacogene Dezaparvovec Compared to Factor IX

Treatment	Drug Cost	Total Cost	Bleeds	QALYs	Life Years	evLYs
Etranacogene Dezaparvovec	$7,494,000*	$8,447,000	182	17.98	27.13	17.98
Factor IX	$14,029,000	$15,809,000	247	17.31	27.13	17.31

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

*These are based on a placeholder cost for etranacogene dezaparvovec of $2,500,000.

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 costs and higher QALYs.

Table 4.4. Incremental Cost-Effectiveness Ratios for the Base Case 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 placeholder cost of etranacogene dezaparvovec of $2,500,000.

Model 2

Table 4.5 below shows the base case results 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 Base-Case for Valoctocogene Roxaparvovec Compared to Emicizumab

Treatment	Drug Cost	Total Cost	Bleeds	QALYs	Life Years	evLYs
Valoctocogene Roxaparvovec	$13,394,000*	$13,834,000	152	17.62	27.13	17.62
Emicizumab	$17,492,000	$18,004,000	153	17.49	27.13	17.49

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 Base Case 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

See the Supplement tables in Section E5 for details. In all of the scenario analyses, using the placeholder prices mentioned above, in model 1, etranacogene dezaparvovec was found to be a dominant treatment. In model 2, valoctocogene roxaparvovec was found to be a dominant treatment except in the case with a cap on savings of $150,000 per year. In that scenario, valoctocogene roxaparvovec was found to not be cost effective.

Threshold Analyses

Table 4.7 below displays the threshold prices at various willingness to pay levels for the base case, as well as for the scenario 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 gains between etranacogene dezaparvovec and factor IX is small, the difference in price across the willingness to pay 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
Etranacogene Dezaparvovec Base Case	$9,896,000	$9,929,000	$9,962,000	$9,995,000
$150,000 Cap Scenario	$2,908,000	$2,941,000	$2,974,000	$3,007,000
Shared Savings (50:50)	$5,079,000	$5,112,000	$5,145,000	$5,178,000
No Savings	$262,000	$295,000	$328,000	$361,000

QALY: quality-adjusted life year

Table 4.8 shows the threshold prices for valoctocogene roxaparvovec. In the capped savings scenario the threshold price is lower than the placeholder price as in that scenario valoctocogene roxaparvovec was not found to be dominant. Also similar to model ,1 because the QALY differences were small between valoctocogene roxaparvovec and emicizumab, the prices across willingness to pay levels are relatively similar.

Table 4.8. QALY-Based Threshold Analysis Results

	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
Valoctocogene Roxaparvovec Base Case	$6,776,000	$6,782,000	$6,789,000	$6,796,000
$150,000 Cap Scenario	$1,931,000	$1,938,000	$1,944,000	$1,951,000
Shared Savings (50:50)	$3,517,000	$3,524,000	$3,530,000	$3,537,000
No Savings	318,000	$324,000	$331,000	$338,000

QALY: quality-adjusted life year

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
- Also, the relationship between joint bleeds and surgery is imperfect and the model assumes one joint surgery at a time
- In addition, utility scores for bleeds come from patients with inhibitors

- Finally, we have placeholder prices for valoctocogene roxaparvovec and for etranacogene dezaparvovec

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 higher QALYs and lower bleeds. In model 2 in the capped cost savings scenario for gene therapy of $150,000, valoctocogene roxaparvovec became not cost effective even at high willingness to pay thresholds, illustrating that the cost saving results for valoctocogene roxaparvovec in hemophilia A were sensitive to the cost of the comparator being well above $150,000 per year. However, in model 1, etranacogene dezaparvovec was found to be a dominant treatment even in the capped cost savings scenario meaning that even if factor IX was priced at $150,000 a year, etranacogene dezaparvovec would still be projected to be a dominant treatment.

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.
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life	Minimal impact as gene therapy currently is offered only to adults who typically manage their own care.
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. This 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.

6. Health Benefit Price Benchmarks

ICER does not provide health benefit price benchmarks as part of draft reports because results may change with revision following receipt of public comments. We therefore caution readers against assuming that the values provided in the Threshold Prices section of this draft report will match the health benefit price benchmarks that will be presented in the next version of this Report.

7. Potential Budget Impact

Upon inspection of the annual undiscounted costs over the first 5 years of therapy when comparing valoctocogene roxaparvovec to emicizumab and etranacogene dezaparvovec to factor IX therapy, it was observed that both gene therapies were cost saving. Therefore, no budget impact analysis was conducted for either valoctocogene roxaparvovec or etranacogene dezaparvovec. While it is possible that there may be a non-negative budget impact associated with either therapy at threshold prices or future health benefit price benchmarks, ICER does not expect either manufacturer to set prices that would begin to approach or resemble threshold or benchmark prices. Refer to Section 4 (Threshold Analyses) for estimates of threshold prices.

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Supplemental Materials

A. Background: Supplemental Information

A1. Definitions

Severe Hemophilia: Factor VIII or IX levels less than 1 percent.[46]

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.[46]

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.[47]

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).[48]

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).[49]

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[50]

The MASAC guidelines state that recombinant factor VIII products are the recommended treatment of choice for patients with hemophilia A. The 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[51]

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[52]

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.[53] 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).[53] 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.[54,55] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[56] 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 ran on June 14, 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 ran on June 14, 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 ran on June 14, 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=20200101-20220613

Search ran on June 14, 2022.

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

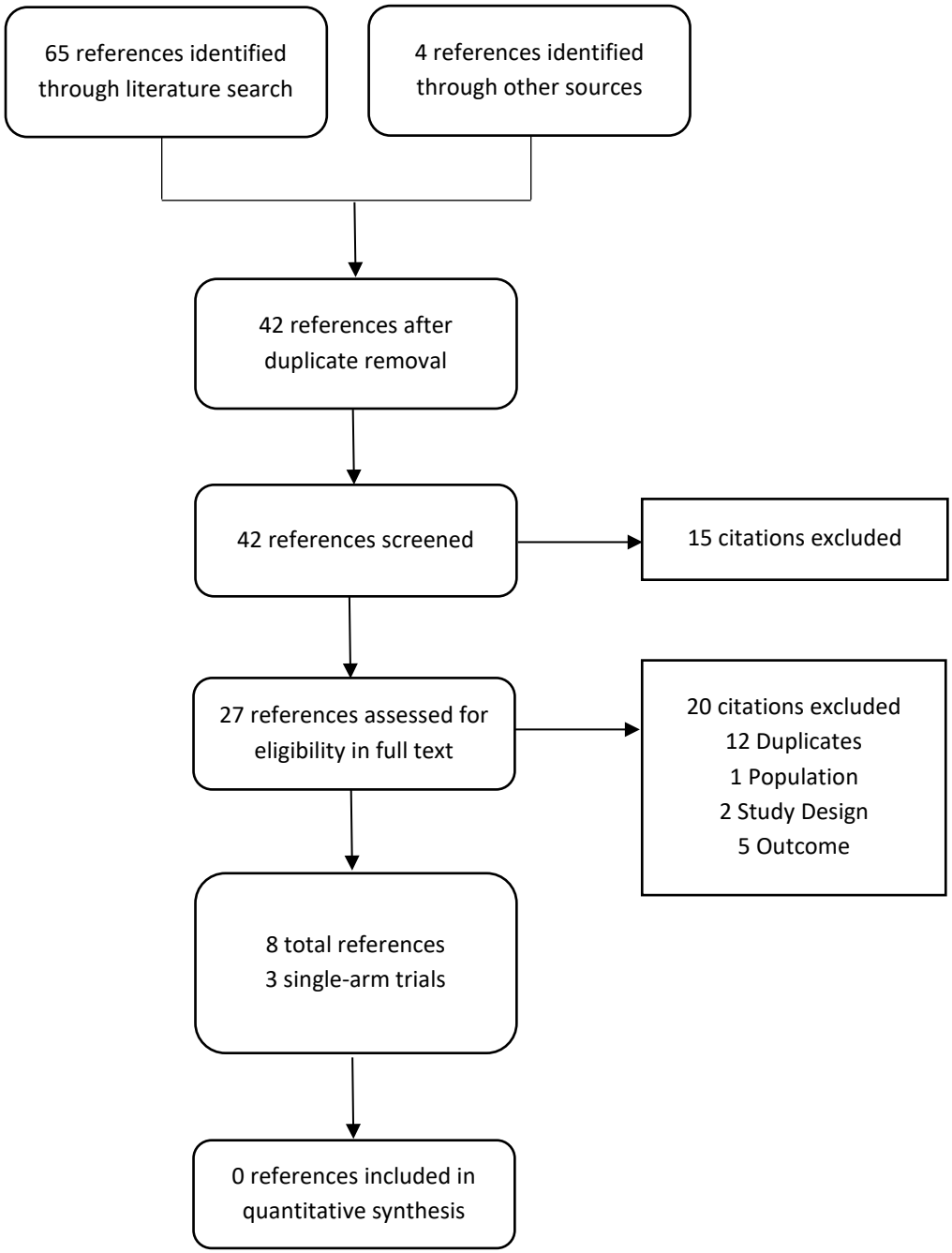
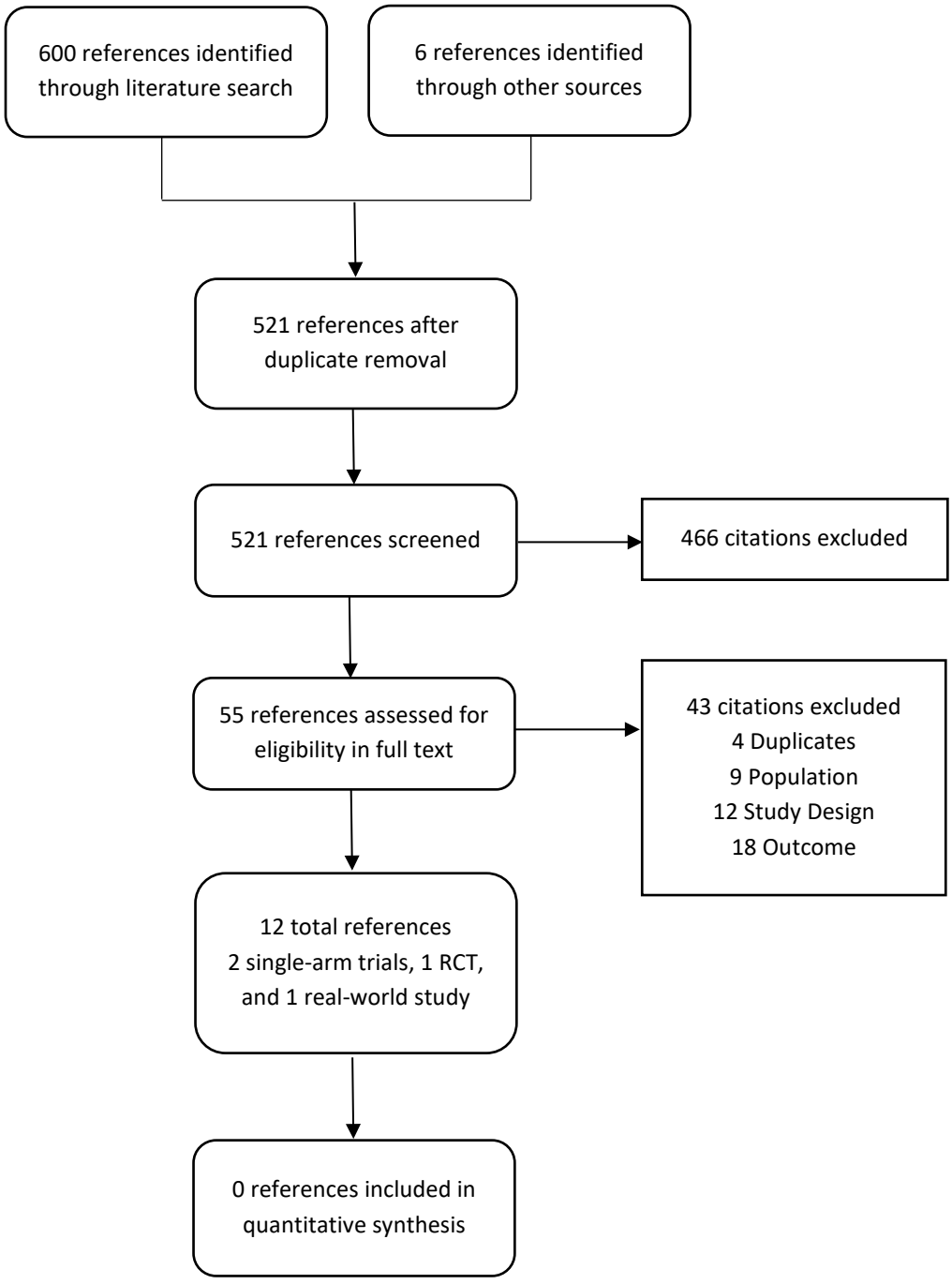


Figure D2. PRISMA Flow Chart: Results of Literature Search for Valoctocogene Roxaparvovec and Emicizumab for Hemophilia A



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.[57,58]

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[9,13-15,29]

		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[12,13,16,29]

		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[9,11,13,14]

			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[9,29]

	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[9,12-14]

		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[9,29]

	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[17,22,24,30,59,60]

		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[17,18,27,30]

		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[22,27,30]

		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[17-19,21,22,59]

		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[17,18]

		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*

		Baseline	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
	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[17,18,21,22,27,30]

		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
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

		Valoctocogene roxaparvovec GENEr8-1 Phase 3	Valoctocogene roxaparvovec BMN 270-201 Phase 1/2	Emicizumab HAVEN 3 Cohort D Phase 3
	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[20,25,27,30]

		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*
	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*

		Baseline Mean (SD)	Post-Treatment Mean (SD)	Mean Change from Baseline (SD); p-value
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 - Treated with gene therapy before	**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
Valoctocogene Roxaparvovec					
Study to Evaluate the Efficacy and Safety of Valoctocogene Roxaparvovec, With Prophylactic Steroids in	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	**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	**Primary** - Change in median FVIII activity [52 weeks] **Secondary** - Change in the annualized utilization (IU/kg) of exogenous FVIII	**Primary:** January 2023 **Study:** January 2027

Hemophilia A (GENEr8-3) BioMarin Pharmaceutical NCT04323098		with prophylactic corticosteroids	- 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	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]	
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**	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	**Primary** - Adverse events [61 months] **Secondary** - FVIII activity at or above 5 IU/dL [26 weeks] - Use of exogenous FVIII replacement therapy [61 months]	**Primary:** November 2027 **Study:** November 2027

NCT03520712			- 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	- Number of bleeding episodes requiring exogenous FVIII therapy [61 months]	

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.
- 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.[32-36] 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.[37,38]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.[37,38]

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.

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.[17,39] 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.[22,40]
- 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 0.02 per cycle as long as patients did not switch therapies based on data submitted by BioMarin.

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.[42]
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 in base-case analyses using a simple average of rates of total joint bleeds to all bleeds seen in the various arms of the HAVEN 3 trial (provided by Genentech) and the proportion seen in the POTTER trial (resulting in 0.66 as the proportion used). [22,40]	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 base case. 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 base case.

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.[39,63] 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.[39,63] 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.

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

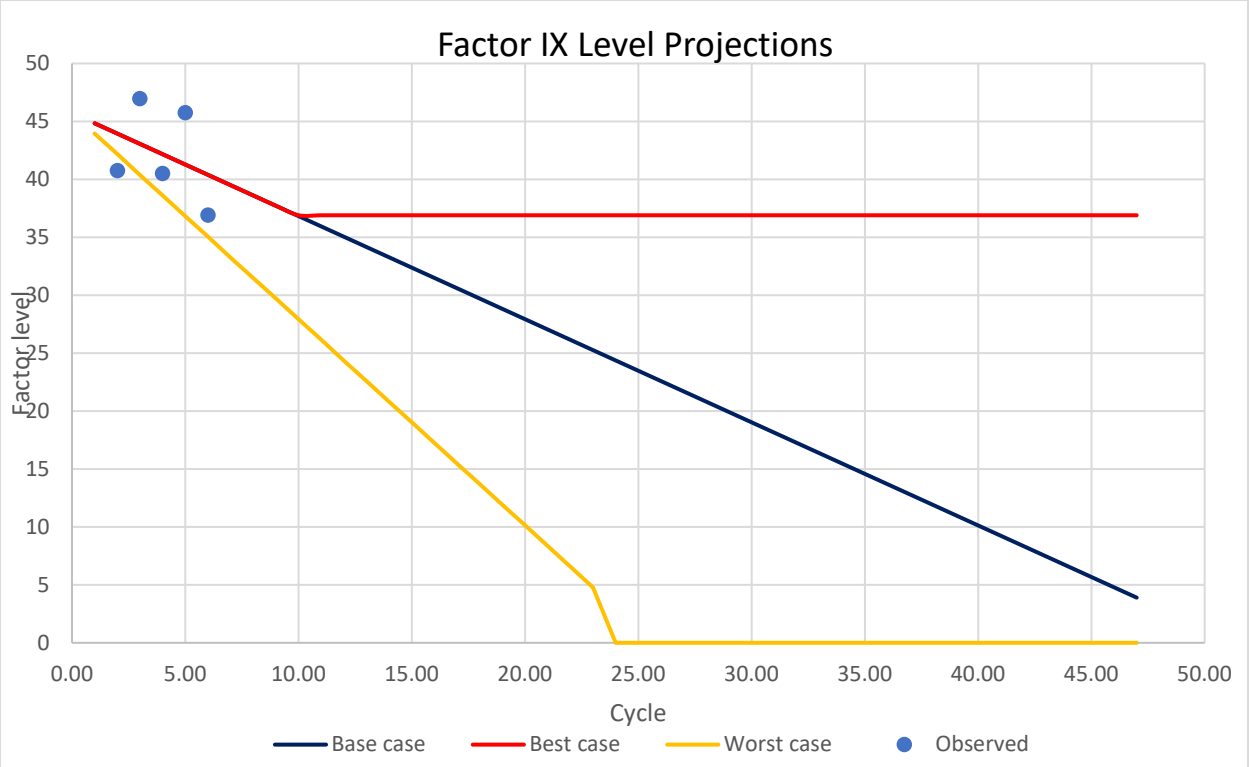


Table E6. Bleed Rates in Hemophilia A for Selected Factor VIII Levels Used to Project Bleeds

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).[39] 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

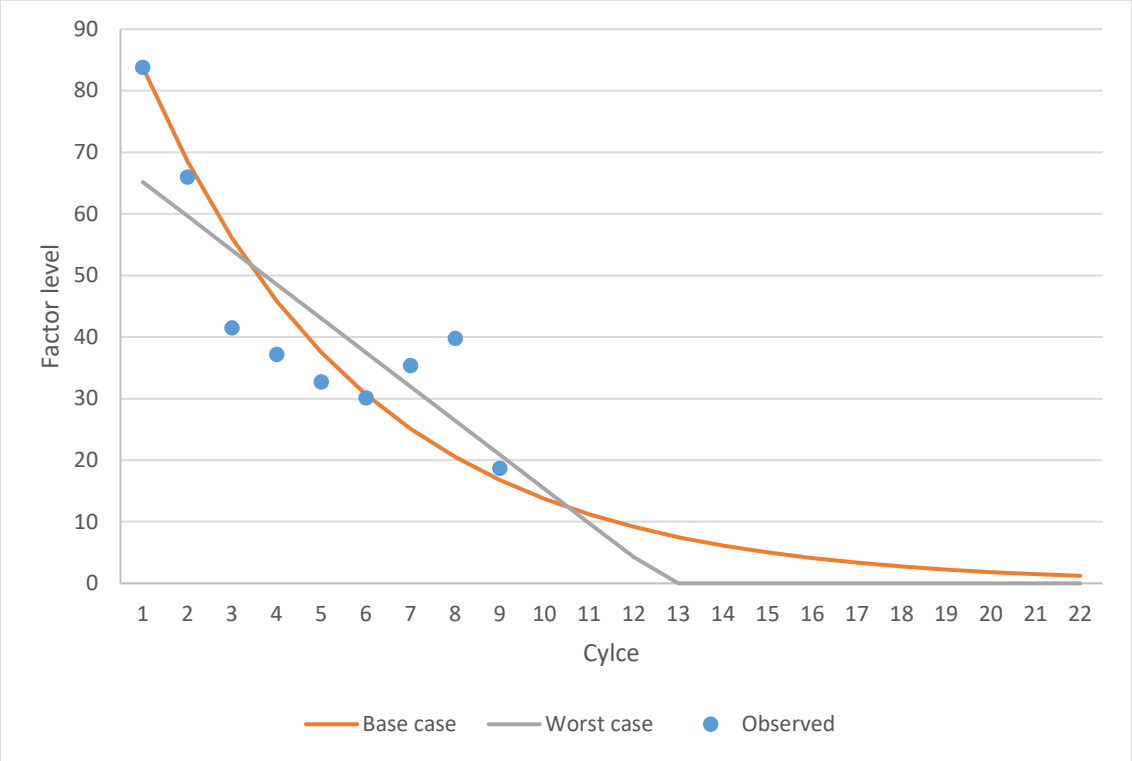
Table E6 above).[39] To begin, we used average bleed rates seen in patient level data in the GENEr8-1 trial but with the following assumptions. To be most consistent with the value-based contract proposed by BioMarin we had 2% of the patients with the highest ABR drop out of the data each year for the 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.[39] 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.[39] 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	2.60	1.72	0.60	0.70
Valoctocogene Roxaparvovec Year 2	0.49	0.32	0.13	0.11
Valoctocogene Roxaparvovec Year 10	7.28	4.82	1.68	1.95
Valoctocogene Roxaparvovec Year 20	2.60	1.72	0.60	0.70

See Figure E2 below for projections of factor VIII levels across time. Note that the optimistic scenario used the base case 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



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 Transition Probabilities Across Pettersson Scores in Model 2

Drug	Age 18-24	Age 25 and Over
Emicizumab	0.016	0.085
Valoctocogene Roxaparvovec Year 1	0.01	N/A
Valoctocogene Roxaparvovec Year 2	0.008	N/A
Valoctocogene Roxaparvovec Year 20	N/A	0.085

Valoctocogene 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 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]

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).[43] 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.[32-34,44] 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.[33,44]

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[44]
31-40	0.74	0.65	O'Hara 2018[66], Laupacis 1993[44]
41-50	0.69	0.61	O'Hara 2018[66], Laupacis 1993[44]
51-60	0.63	0.56	O'Hara 2018[66], Laupacis 1993[44]
61 and over	0.54	0.48	O'Hara 2018[66], Laupacis 1993[44]

*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.[32,34] 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).[32] 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.[32]]

Table E10. Bleed-Related Disutilities

Bleed Type	Disutility per Cycle*	Source
Bleed Not Into a Target Joint	-0.002	Neufeld 2012[32]
Target Joint Bleed	-0.003	Mazza 2016[34]

*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 both gene therapies in their respective models based on EQ5D data provided by BioMarin and CSL Behring.

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).[43,71]

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[43], 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

Base-Case Results

Model 1

Table E14 below shows the base case results for model 1 with a placeholder price for etranacogene dezaparvovec of $2,500,000. 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 Base-Case for Etranacogene Dezaparvovec Compared to Factor IX

Treatment	Drug Cost	Total Cost	Bleeds	QALYs	Life Years	evLYs
Etranacogene Dezaparvovec	$7,494,000*	$8,447,000	182	17.98	27.13	17.98
Factor IX	$14,029,000	$15,809,000	247	17.31	27.13	17.31

*Based on a placeholder cost for etranacogene dezaparvovec of $2,500,000

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 Base Case

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 base case 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 Base-Case for Valoctocogene Roxaparvovec Compared to Emicizumab

Treatment	Drug Cost	Total Cost	Bleeds	QALYs	Life Years	evLYs
Valoctocogene Roxaparvovec	$13,394,000*	$13,834,000	152	17.62	27.13	17.62
Emicizumab	$17,492,000	$18,004,000	153	17.49	27.13	17.49

*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 Base Case

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

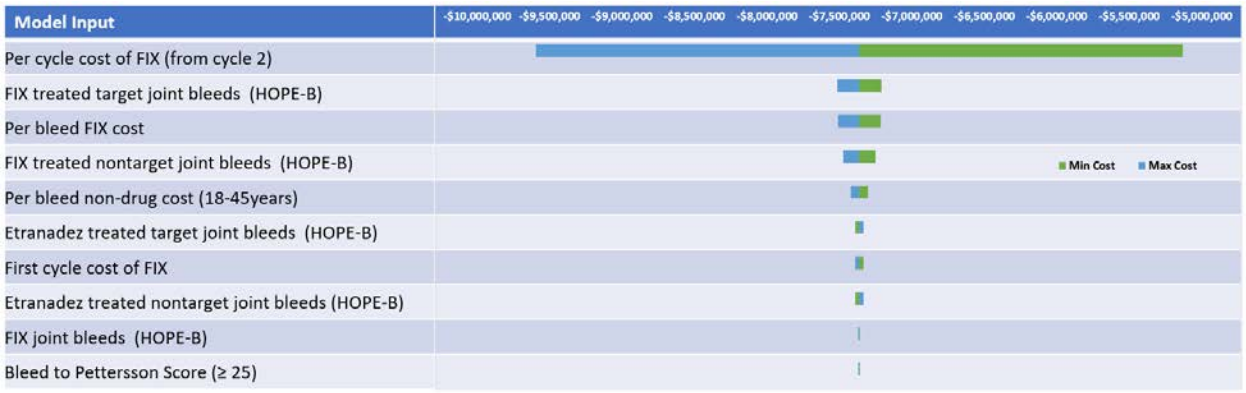


Table E18. Inputs and Results for Etranacogene Dezaparvovec versus FIX cost Tornado Diagram

Inputs	Low Input Value	High Input Value	Minimum Cost	Maximum Cost
Per cycle cost of FIX (from cycle 2)	$177,312	$295,520	-$5,131,311	-$9,593,931
FIX treated target joint bleeds (HOPE-B)	1.60	2.66	-$7,208,387	-$7,516,855
Per bleed FIX cost	$8,177	$13,629	-$7,217,284	-$7,507,957
FIX treated nontarget joint bleeds (HOPE-B)	1.14	1.90	-$7,252,557	-$7,472,684
Per bleed non-drug cost (18-45years)	$3,624	$6,040	-$7,303,177	-$7,422,064
Etranacogene dezaparvovec treated target joint bleeds (HOPE-B)	0.33	0.55	-$7,392,790	-$7,332,451
First cycle cost of FIX	$177,312	$295,520	-$7,335,169	-$7,390,073
Etranacogene dezaparvovec treated nontarget joint bleeds (HOPE-B)	0.30	0.50	-$7,390,047	-$7,335,194
FIX joint bleeds (HOPE-B)	1.76	2.94	-$7,359,267	-$7,366,072
Bleed to Pettersson Score (≥ 25)	4.89	8.15	-$7,366,903	-$7,360,151

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	Minimum QALY	Maximum QALY
Per cycle utility gain in gene therapy arm	0.023	0.038	0.531	0.795
FIX treated target joint bleeds (HOPE-B)	1.598	2.663	0.635	0.691
Disutility of bleeding in a target joint (per cycle)	0.002	0.004	0.641	0.685
FIX treated nontarget joint bleeds (HOPE-B)	1.140	1.900	0.650	0.676
Health state utility at age greater than 60 and PS 1-28	0.405	0.675	0.651	0.675
Health state utility at age greater than 60 and after surgery	0.362	0.603	0.674	0.652
Disutility of bleeding in a nontarget joint (per cycle)	0.002	0.003	0.653	0.673
Etranacogene dezaparvovec treated target joint bleeds (HOPE-B)	0.330	0.550	0.668	0.657
Etranacogene dezaparvovec treated nontarget joint bleeds (HOPE-B)	0.300	0.500	0.666	0.660
FIX joint bleeds (HOPE-B)	1.763	2.938	0.661	0.665

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

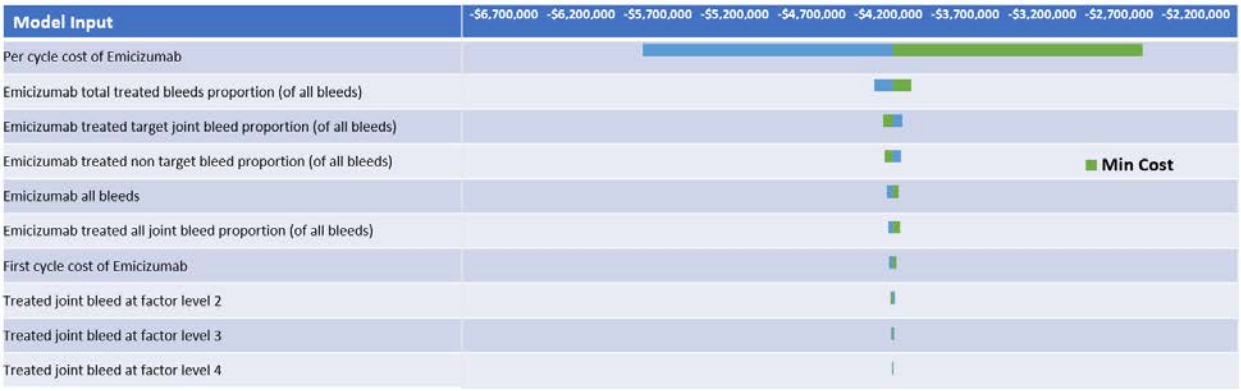


Table E21. Inputs and Results for Valoctocogene Roxaparvovec versus Emicizumab cost Tornado Diagram

Input	Low Input Value	High Input Value	Minimum Cost	Maximum Cost
Per cycle cost of Emicizumab	$220,557	$367,596	-$2,542,714	-$5,797,824
Emicizumab total treated bleeds proportion (of all bleeds)	$0	$1	-$4,051,133	-$4,289,406
Emicizumab treated target joint bleed proportion (of all bleeds)	0.20	0.34	-$4,232,004	-$4,108,535
Emicizumab treated non target bleed proportion (of all bleeds)	0.17	0.29	-$4,223,185	-$4,117,354
Emicizumab all bleeds	1.95	3.25	-$4,130,162	-$4,209,994
Emicizumab treated all joint bleed proportion (of all bleeds)	0.26	0.43	-$4,121,849	-$4,199,319
First cycle cost of Emicizumab	$254,489	$424,149	-$4,148,340	-$4,192,199
Treated joint bleed at factor level 2	2	3	-$4,185,183	-$4,155,357
Treated joint bleed at factor level 3	1.89	3.15	-$4,178,014	-$4,162,525
Treated joint bleed at factor level 4	1	2	-$4,174,746	-$4,165,793

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

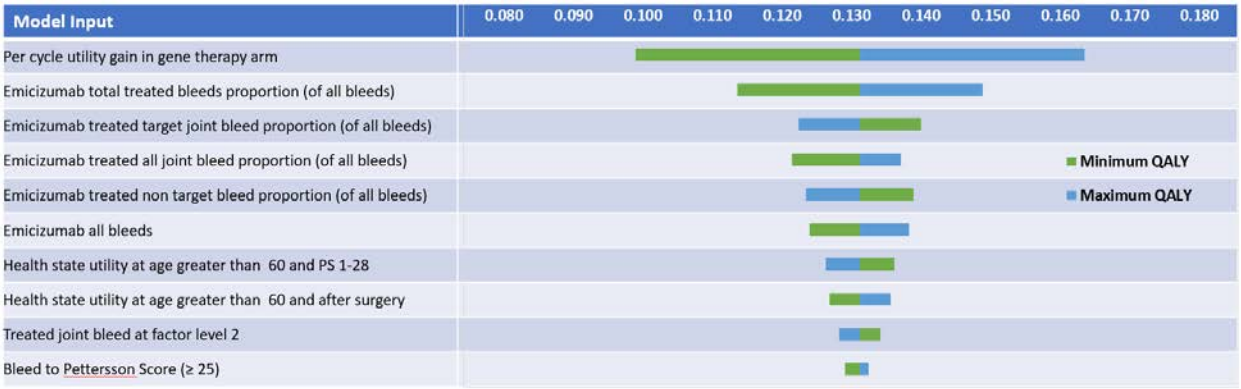


Table E22. Inputs and Results for Valoctocogene Roxaparvovec versus Emicizumab QALY Tornado Diagram

Input	Low Input Value	High Input Value	Minimum QALY	Maximum QALY
Per cycle utility gain in gene therapy arm	0.009	0.015	0.099	0.163
Emicizumab total treated bleeds proportion (of all bleeds)	0.375	0.625	0.114	0.149
Emicizumab treated target joint bleed proportion (of all bleeds)	0.202	0.337	0.140	0.122
Emicizumab treated all joint bleed proportion (of all bleeds)	0.260	0.433	0.121	0.137
Emicizumab treated non target bleed proportion (of all bleeds)	0.173	0.288	0.139	0.123
Emicizumab all bleeds	1.950	3.250	0.124	0.138
Health state utility at age greater than 60 and PS 1-28	0.405	0.675	0.136	0.126
Health state utility at age greater than 60 and after surgery	0.362	0.603	0.127	0.136
Treated joint bleed at factor level 2	1.890	3.150	0.134	0.128
Bleed to Pettersson Score (≥ 25)	4.890	8.150	0.129	0.132

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 analyse 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.
Finally, a scenario where all patients switch treatment at a projected factor level of 5 IU/mL.

In addition we conducted the following additional scenario analyses following the ICER SST framework. The scenario analyses will include the following:

Extending duration of disutility from bleeds to 7 full days from 2 full days and 5 half days.
Doubling the bleed rates for patients with arthropathy across all treatments.
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.

As both treatments meet ICERs Single or Short-Term Transformative (SST) framework, the following scenarios will also be 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. We also did a scenario with no savings to the health system from the gene therapy.

Optimistic and conservative assumptions regarding the benefit of treatment, to be presented in conjunction with the base case. *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.*

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

Tables E24and E25 show the non SST and the SST scenario results. All have etranacogene dezaparvovec as dominant at a placeholder price of $2,500,000

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^-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.	Dominant
Optimistic assumptions regarding the benefit of treatment, to be presented in conjunction with the base case.	Dominant
Conservative assumptions regarding the benefit of treatment, to be presented in conjunction with the base case.	Dominant
Zero net savings.	$3,426,000

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 valoctocogene roxaparvovec was found to be dominant. In the $150,000 cap scenario, 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^-1.	Dominant

PS: Pettersson Score

Table E27. Non-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.	$4,362,231
Optimistic assumptions regarding the benefit of treatment, to be presented in conjunction with the base case.	Dominant
Conservative assumptions regarding the benefit of treatment, to be presented in conjunction with the base case.	Dominant
Zero net savings.	$16,594,000

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	$1,875,000	$3,125,000	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	1.95	3.25	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 in cycle 0 (Valoctocogene roxaparvovec)	0.32	0.53	Uniform
Bleed HR in cycle 1 (Valoctocogene roxaparvovec) (compared to cycle 0)	0.55	0.92	Uniform
Bleed HR in cycle 2 (Valoctocogene roxaparvovec) (compared to cycle 0)	0.47	0.79	Uniform
Bleed HR in cycle 3 (Valoctocogene roxaparvovec) (compared to cycle 0)	0.41	0.69	Uniform
Bleed HR in cycle 4 (Valoctocogene roxaparvovec) (compared to cycle 0)	0.36	0.60	Uniform
Bleed HR in cycle 5 (Valoctocogene roxaparvovec) (compared to cycle 0)	0.31	0.52	Uniform
Bleed HR in cycle 6 (Valoctocogene roxaparvovec) (compared to cycle 0)	0.27	0.46	Uniform
Bleed HR in cycle 7 (Valoctocogene roxaparvovec) (compared to cycle 0)	0.25	0.41	Uniform
Bleed HR in cycle 8 (Valoctocogene roxaparvovec) (compared to cycle 0)	0.22	0.36	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	0.01	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. Heterogeneity and Subgroups

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

E7. 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.