Valoctocogene Roxaparvovec and Emicizumab for Hemophilia A: Effectiveness and Value

Draft Evidence Report

August 26, 2020

Prepared for

NEW ENGLAND CEPAC
COMPARATIVE EFFECTIVENESS PUBLIC ADVISORY COUNCIL
AN ICER PROGRAM

ICER Staff	University of Illinois at Chicago College of Pharmacy Modeling Group
David M. Rind, MD, MSc Chief Medical Officer ICER **Foluso Agboola, MBBS, MPH** Director, Evidence Synthesis ICER **Serina Herron-Smith, BS** Research Assistant ICER **Rick Chapman, PhD, MS** Director of Health Economics ICER **Steven D. Pearson, MD, MSc** President ICER **Pamela Bradt, MD, MPH** Chief Scientific Officer ICER	**Surrey M. Walton, PhD** Associate Professor, Pharmacy Systems, Outcomes and Policy Assistant Director, Center for Pharmacoepidemiology and Pharmacoeconomic Research University of Illinois at Chicago College of Pharmacy **Danny Quach, PharmD** University of Illinois at Chicago College of Pharmacy *The role of the University of Illinois (UIC) College of Pharmacy Modeling Group is limited to the development of the cost-effectiveness model, and the resulting ICER reports do not necessarily represent the views of the UIC.*

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

About ICER

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

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The New England Comparative Effectiveness Public Advisory Council (New England CEPAC) – a core program of ICER – provides a public venue in which the evidence on the effectiveness and value of health care services can be discussed with the input of all stakeholders. The New England CEPAC seeks to help patients, clinicians, insurers, and policymakers interpret and use evidence to improve the quality and value of health care.

The New England CEPAC Council is an independent committee of medical evidence experts from across New England, with a mix of practicing clinicians, methodologists, and leaders in patient engagement and advocacy. All Council members meet strict conflict of interest guidelines and are convened to discuss the evidence summarized in ICER reports and vote on the comparative clinical effectiveness and value of medical interventions. More information about the New England CEPAC is available at https://icer-review.org/programs/new-england-cepac/.

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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 clinical experts provided input that helped guide the ICER team as we shaped our scope and report. None of these individuals is responsible for the final contents of this report or should be assumed to support any part of this report, which is solely the work of the ICER team and its affiliated researchers.

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

Expert Reviewers

Steven Pipe, MD
Professor of Pediatrics and Pathology
Pediatric Medical Director, Hemophilia and Coagulation Disorders Program
Director, Special Coagulation Laboratory
University of Michigan
Dr. Pipe has received consulting fees from Apcintex, Bayer, BioMarin, Catalyst Biosciences, CSL Behring, HEMA Biologics, Freeline, Novo Nordisk, Pfizer, Roche/Genentech, Sangamo Therapeutics, Sanofi, Takeda, Spark Therapeutics, uniQure.

Margaret V. Ragni, MD, MPH
Professor of Medicine and Clinical and Translational Science
Director, Hemophilia Center of Western PA
University of Pittsburgh Medical Center
Dr. Ragni receives research funding (through the University of Pittsburgh) for gene therapy trials with SPARK, a gene therapy trial with BioMarin, and past gene therapy trial funding with Sangamo.

Mark W. Skinner, JD
President & CEO
Institute for Policy Advancement Ltd.
Mr. Skinner has received fees and honoraria of more than $5,000 for educational presentations and advisory board participation from F. Hoffman-La Roche / Genentech, Bayer Healthcare, BioMarin, and the Blue Cross Blue Shield Association. Mr. Skinner's household has or held equity interests in the following companies in the health sector: Cryosport, CVS Health, Editas Medicine, Horizon discovery, Illumina, Intellia Therapeutics, Intuitive Surgical, Johnson & Johnson (Sold), Novartis, Regeneron (Sold) and Teladoc Health. These holdings are independently managed by a financial advisor with instructions not to invest in companies with a known interest in therapies for bleeding disorders. Mr. Skinner is a 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.

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List of Acronyms 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**

1. Introduction

1.1 Background

Background

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

Hemophilia A is a condition of increased tendency to bleed due to an inherited deficiency of factor VIII, which disrupts the clotting cascade (Figure 1). Hemophilia A has X-linked recessive inheritance, and so predominately affects males. It is the most common of the hemophilias with an incidence of one in 5,000 male births.[1] The exact prevalence of hemophilia in the United States (US) is not known, but is estimated to be around 20,000.[2] Approximately 77% of all hemophilia patients in the US have hemophilia A.[3]

Patients with hemophilia A, particularly those with severe disease, are at risk for life-threatening bleeding, including intracranial bleeding, but bleeding into a joint (hemarthrosis) or muscle is more common and can lead to substantial disability.[4] Hemarthroses cause ongoing joint inflammation and damage and also increase the likelihood of further bleeding into the same joint.

Severity of hemophilia A has generally been defined by factor levels (the percentage of normal factor that a patient has).[5] However, severity based on factor levels does not perfectly correlate with actual clinical severity.[6] Despite this, other severity classifications are not yet widely accepted, and factor levels define severity in most clinical trials. Using factor level classifications, severe disease is defined by factor VIII levels below 1% of normal.[5] Patients with severe disease who are not receiving prophylactic treatment experience an average of 20 to 30 episodes of spontaneous bleeding or excessive bleeding after minor trauma per year.[1] Patients with moderate disease (factor VIII levels of 1% to 5% of normal) typically have delayed bleeding episodes after minor trauma several times per year, but only occasionally have spontaneous bleeding.[7] Individuals with mild disease (factor VIII levels between 6% to 40% of normal) typically have bleeding after procedures such as tooth extractions or surgery, or after significant injuries.

To reduce the risk of bleeding, patients with severe hemophilia A have typically administered factor VIII concentrate intravenously multiple times per week.[7,8] The use of factor concentrates both as treatment and prophylaxis has dramatically altered the management and clinical course of patients with hemophilia A. However, prophylaxis with factor replacement is burdensome and does not maintain patients at normal levels of factor VIII. A number of factor VIII preparations are available

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

Unfortunately, along with the advances in treatment of hemophilia A and B, the products used in the 1970s and 1980s were contaminated with viruses; of particular importance, HIV and hepatitis C (widespread hepatitis B testing of donor blood used to manufacture blood products occurred by 1975 and hepatitis B vaccine, developed in the 1980s, provided further protection from HBV transmission via blood products). Although by the mid-1980s testing for antibodies to HIV and treatment of donor blood used to manufacture blood products dramatically improved the safety of these products, people with hemophilia treated prior to this time were very likely to develop infection. AIDS resulted in the deaths of thousands of patients with hemophilia A before effective treatment became available in the late 1990s.[9] Hepatitis C, a more indolent virus, led to cirrhosis and death in many additional patients, and only in recent years has a highly effective and tolerable treatment for hepatitis C been developed.

Administration of Factor VIII

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

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

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

Not surprisingly, adherence to an intravenous therapy that must be administered frequently can be difficult for patients who are appropriate candidates for prophylaxis. Only 50%-70% of patients adhere to prophylaxis regimens, particularly once they are old enough to make treatment decisions for themselves.[10,11]

Emicizumab

Emicizumab-kxwh (Hemlibra®, Genentech, referred to as "emicizumab" in this Report) is a monoclonal antibody with dual targets ("bispecific") that allow it to bridge activated factor IX and factor X, the role normally played by activated factor VIII in the clotting cascade (Figure 1).[12] Emicizumab was approved by the US Food and Drug Administration (FDA) as a prophylactic treatment for hemophilia A in patients who have inhibitors to factor VIII in 2017 and in those without inhibitors in 2018.[13] Emicizumab is administered subcutaneously and may be dosed weekly, every two weeks, or every four weeks based on provider and patient preference.

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

Prior to the approval of emicizumab, patients who developed inhibitors to factor VIII that could not be eradicated required bypassing agents such as activated prothrombin complex concentrate or recombinant activated factor VIII administered frequently and at high cost for prophylaxis.[14-16] Patients with inhibitors who require treatment for bleeding while receiving emicizumab will generally be treated with a bypassing agent as on-demand therapy and treatment of a single bleeding episode can cost $50,000 or more.[15,16] ICER found in 2018 that in patients with factor inhibitors, prophylaxis with emicizumab was cost saving (Emicizumab for Hemophilia A with Inhibitors: Effectiveness and Value), even though the wholesale acquisition cost (WAC) of emicizumab was approximately $482,000 for the first year of treatment and $448,000 for subsequent years at the time. Patients with Factor inhibitors are not included in this current review.

Valoctocogene Roxaparvovec

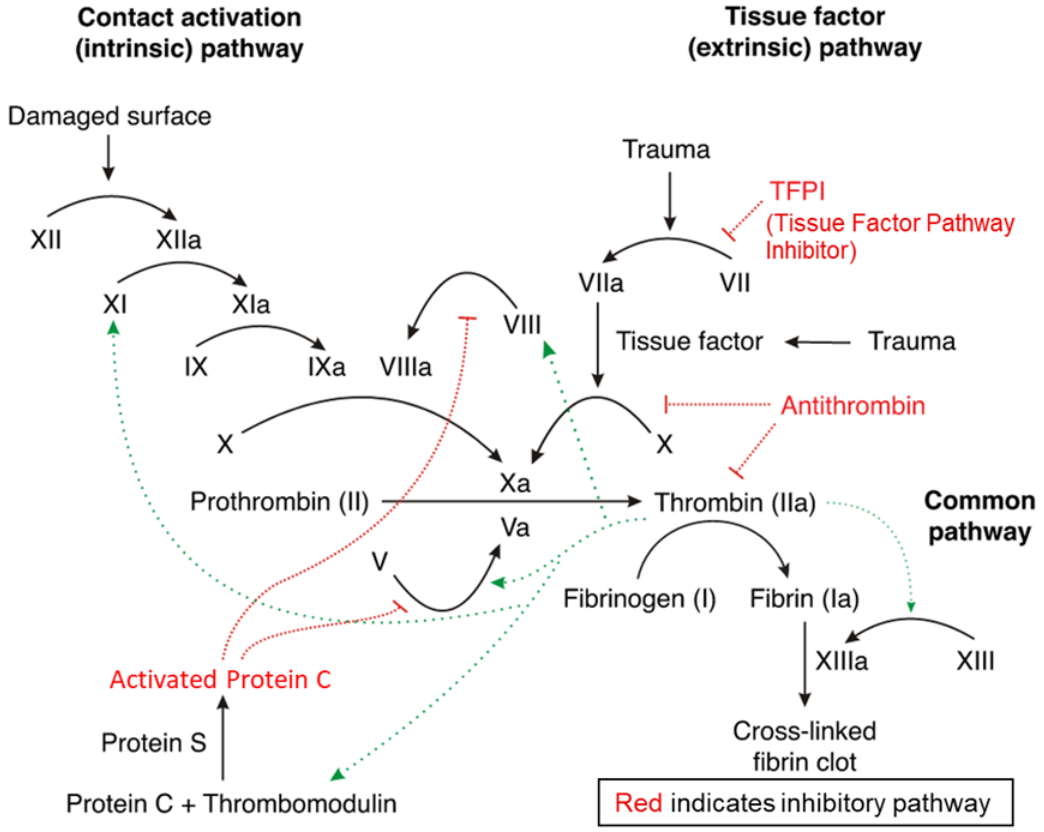
Valoctocogene roxaparvovec (Roctavian; BioMarin) is an adeno-associated virus serotype 5 (AAV5) mediated liver-directed gene therapy for hemophilia A.[17] Gene therapy for hemophilia A is difficult because of the size of the factor VIII gene. The complete gene is too large to fit into an AAV capsid. Valoctocogene roxaparvovec delivers a B-domain-deleted factor VIII gene with a liver-specific transcription promotor as a mixture of 5' or 3' incomplete strands in each capsid that must then anneal to form the full length B-domain-deleted gene required for production of factor VIII.[17,18] Although liver production of factor VIII normally occurs in liver sinusoid endothelial cells, the target of valoctocogene roxaparvovec is hepatocytes.[19] Thus gene therapy with valoctocogene roxaparvovec results in factor VIII production in the liver, but not in the cells in the liver that normally produce factor VIII.

Published information is available on a limited number of patients who received therapy with valoctocogene roxaparvovec, with up to three years of follow-up. Public presentations have some

information after four years of follow-up and on a subset of patients in a phase III trial of valoctocogene roxaparvovec.

BioMarin submitted a biologics license application for valoctocogene roxaparvovec to the FDA in December 2019 and received a Complete Response Letter (CRL) rejecting approval in August 2020.[20] As a result of this FDA decision and the expectation that two years of additional data on valoctocogene roxaparvovec will be available prior to future FDA consideration for approval, ICER considers all results in this report related to valoctocogene roxaparvovec, including results on comparative effectiveness and cost effectiveness, to be highly preliminary. ICER will not be suggesting health benefit price benchmarks for valoctocogene roxaparvovec nor will analyses be performed to evaluate potential budget impact. Nonetheless, ICER believes that it is in patients' and the public interest to publish the preliminary findings of the review to support future discussions and decisions regarding how best to generate and assess evidence on the clinical and cost-effectiveness of valoctocogene roxaparvovec.

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



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

1.2 Scope of the Assessment

The scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence was sought from randomized controlled trials as well as high-quality systematic reviews; observational studies and case series were considered for inclusion as well, given the limited evidence base for valoctocogene roxaparvovec.

Populations

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

Interventions

The interventions of interest for this review are listed below:

- Valoctocogene roxaparvovec
- Emicizumab

Comparators

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

Outcomes

We looked for evidence on the following outcomes of interest:

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

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

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

Timing

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

Settings

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

1.3 Definitions

Target Joint: This term is used to describe a joint that has had recurrent bleeding. The exact definition varies, but it is commonly defined as a joint that has had three or more spontaneous bleeds within a consecutive six-month period.[5]

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.[21]

Hemophilia Quality of Life Index for Adults (Haem-A-QoL): A hemophilia-specific, validated, 46-item instrument used to assess the health-related quality of life in adult patients. It is based on a total score transformed to a scale of 0 to 100, with lower scores reflecting better health-related quality of life.[22]

1.4 Research, Development, and Manufacturing Costs

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

1.5 Potential Cost-Saving Measures in Hemophilia A

As described in its Value Assessment Framework for 2020-2023, ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/wp-content/uploads/2019/05/ICER_2020_2023_VAF_013120-2.pdf). These services are not ones that would be directly affected by gene therapy or emicizumab (e.g., fewer bleeds), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of hemophilia beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

2. Patient Perspectives

2.1 Methods

During ICER's scoping and open input periods, we received public comment submissions from 8 stakeholders (3 patient advocacy groups, 4 manufacturers, and 1 multi-stakeholder group) and participated in conversations with 11 key informants (3 patients, 2 patient advocacy groups, 3 manufacturers, and 5 clinical experts). Some stakeholders played more than one role in our outreach. These comments and conversations, along with ICER's 2018 report on emicizumab for hemophilia A, helped us to discuss the impact on patients as described below.

2.2 Impact on Patients

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

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

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

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

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

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

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

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

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

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

3. Summary of Coverage Policies and Clinical Guidelines

3.1 Coverage Policies

We reviewed the Tufts Medical Center Specialty Drug Evidence and Coverage (SPEC) Database for its US commercial health plans' coverage policies for emicizumab (HEMLIBRA®, Genentech), current as of April 2020.[23] Developed by the Center for Evaluation of Value and Risk in Health, the SPEC database features data on more than 290 specialty drugs, more than 175 disease areas, and more than 25,000 decisions from the following 17 largest US national and regional commercial payers: Aetna, Anthem, Blue Cross Blue Shield (BCBS) of Florida (FL), Massachusetts (MA), Michigan (MI), North Carolina (NC), New Jersey (NJ), and Tennessee (TN), CareFirst, Centene, Cigna, Emblem, Health Care Service Corporation (HCSC), Highmark, Humana, Independence Blue Cross (IndepBC), and UnitedHealthcare (UHC).

On August 18, 2020, the FDA issued a Complete Response Letter to BioMarin's Biologic License Application for valoctocogene roxaparvovec, precluding a survey of its coverage policies.[20]

Emicizumab

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

Table 3.1. Representative Private Payer Policies for Emicizumab

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

FDA: Food and Drug Administration

3.2 Clinical Guidelines

National Hemophilia Foundation, Medical and Scientific Advisory Council (MASAC) Recommendations, Recommendation on the Use and Management of Emicizumab-kxwh (Hemlibra®) for Hemophilia A with and without Inhibitors, March 2020[24]

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

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

World Federation of Hemophilia, Guidelines for the Management of Hemophilia, July 2012[25]

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

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

For patients with a severe phenotype of hemophilia A without inhibitors, the WFH recommends prophylaxis with emicizumab to 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[26]

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.

4. Comparative Clinical Effectiveness

4.1 Overview

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

4.2 Methods

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on new therapies for hemophilia A without factor VIII inhibitors followed established best research methods.[27,28] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[29] The PRISMA guidelines include a checklist of 27 items, which are described further in Appendix Table A1.

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

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

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

Study Selection

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

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

Data Extraction and Quality Assessment

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

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus (see Appendix D).[30,31]

Data Synthesis and Statistical Analyses

Data on relevant outcomes were summarized in evidence tables (see Appendix Tables D.1. and D.2.) and synthesized quantitatively and qualitatively in the body of the review. Based on the availability of data from sufficiently similar trials, network meta-analyses (NMAs) were conducted to compare emicizumab with factor VIII prophylaxis on the following outcomes of interest: rates of treated bleeding events and rates of treated joint bleeding. Due to major differences in study design and study characteristics, we did not conduct NMAs to compare valoctocogene roxaparvovec to emicizumab or factor VIII prophylaxis. All NMAs were conducted in a Bayesian framework with random effects on the treatment parameters using the gemtc package in R.[32] The outcomes analyzed were all rate ratios and were analyzed using a Poisson likelihood and the log link function.

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

4.3 Results

Study Selection

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

Of the 16 references, six references (3 publications and 3 conference abstracts)[33-38] corresponded to three unique Phase III trials (1 randomized and 2 non-randomized) of emicizumab.

Five of the references (2 publications, 2 conference presentations, and 1 press release)[17,18,39-41] corresponded to two non-randomized trials of valoctocogene roxaparvovec gene therapy (one Phase I/II and one Phase III).

In addition, we identified five references corresponding to four factor VIII trials that could potentially inform an indirect comparison of factor VIII prophylaxis to emicizumab.[42-46] Following further evaluation of these trials, only one (SPINART) was found to be sufficiently similar to the randomized trial of emicizumab in terms of baseline characteristics, study design and outcome definition to permit NMA.[45,46] Reasons for excluding the other three randomized trials of factor VIII prophylaxis are presented in Appendix Tables D3 and D4.

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

Quality of Individual Studies

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

Assessment of Publication Bias

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

Trials of Emicizumab

We identified three trials of emicizumab that met our inclusion criteria (Table 4.1). We did not identify any RCTs directly comparing emicizumab to factor VIII prophylaxis or valoctocogene roxaparvovec gene therapy.

Key Trial of Emicizumab

HAVEN 3

Evidence to inform our assessment of emicizumab in patients with severe hemophilia without inhibitors was mainly derived from HAVEN 3, a Phase III, open-label, multicenter RCT.[33] The trial enrolled 152 male patients aged 12 years and older with severe hemophilia without factor VIII inhibitors who were receiving on-demand or prophylactic factor VIII treatments. Patients who received treatment for thromboembolic disease within the last 12 months or were currently symptomatic with thromboembolic disease were excluded.

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

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

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

Other Trials of Emicizumab

HAVEN 4

We also identified two non-randomized trials of emicizumab (HAVEN 4 and HOHOEMI).[35] HAVEN 4 was an open label, multicenter, non-randomized Phase III study conducted in patients aged 12 years or older with severe hemophilia A with or without inhibitors to FVIII, previously on on-demand or prophylactic FVIII.[35] The study consisted of a preliminary run-in period to establish pharmacokinetics in seven patients, and a subsequent expansion phase to assess efficacy and safety in 41 patients. Patients were given 6 mg/kg emicizumab every 4 weeks (preceded by four loading doses of 3 mg/kg weekly) and followed up for at least at least 24 weeks. At baseline, 98% of patients had severe hemophilia A, 12% had FVIII inhibitor, 61% had one or more target joint, and 73% were on prophylaxis. The outcomes evaluated included rate of treated bleeds, health-related quality of life, and AEs.

HOHOEMI

HOHOEMI was also an open label, multicenter, non-randomized study conducted in 13 Japanese children 12 years or younger (weighing > 3 kg) who had severe hemophilia A without FVIII inhibitors.[36] Patients were administered four loading doses of 3 mg/kg emicizumab every week followed by maintenance doses of 3 mg/kg every 2 weeks (n=6) or 6 mg/kg every 4 weeks (n=7). The median age was 5.4 years (range: 4 months to 10 years), and only one patient had developed a target joint at baseline. All patients but one (a 4-month old baby) had been on Factor VIII prophylaxis prior to the study. The outcomes evaluated included rate of treated bleeds, caregiver's preference, and AEs.

Table 4.1. Trials of Emicizumab in Hemophilia A Without Inhibitors

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

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

Clinical Benefits of Emicizumab

As described above, we did not identify any RCTs directly comparing emicizumab to Factor VIII prophylaxis or valoctocogene roxaparvovec gene therapy. However, we identified one RCT (SPINART) that allowed us to indirectly compare emicizumab to Factor VIII prophylaxis.[45,46]

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

SPINART was found to be sufficiently similar to HAVEN 3 in terms of baseline characteristics, study design and outcome definitions to allow NMA (see Table 4.2). The major difference noted between the two trials was the study durations (6 months vs. 3 years). However, this was not expected to affect NMAs of bleeding rates, as these outcomes were annualized. As an example, results from the SPINART trial showed similar annualized bleeding rate ratio on treated bleeds for Factor VIII

prophylaxis versus no prophylaxis at 1.7 years (rate ratio [RR]: 0.06; 95% CI: NR) and at three years (RR: 0.06; 95% CI: 0.04, 0.1) (See Appendix Tables D7 and D8).

Table 4.2. Key Trial of Emicizumab (HAVEN 3) and FVIII Prophylaxis (SPINART)

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

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

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

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

In the HAVEN 3 trial, there were fewer treated bleeds among patients randomized to emicizumab weekly (ABR 1.5) or every two weeks (ABR 1.3) compared to the no-prophylaxis group (ABR 38.2) (RR=0.04, 95% CI: 0.02,0.08 and RR=0.03, 95% CI: 0.02,0.07, respectively) (Table 4.3).[33] Approximately 60% of patients randomized to emicizumab had no bleeding during the follow up period; all patients in the no prophylaxis group had bleeding events. Similarly, differences in favor of emicizumab compared to no prophylaxis were observed in the rates of other secondary bleeding related endpoints including all bleeding events, treated spontaneous bleeds, treated joint bleeds, and treated target joint bleeds (see Table 4.3).

In SPINART, there were fewer treated bleeds at three years among patients randomized to recombinant factor VIII (Kogenate FS) prophylaxis group compared to the no-prophylaxis group (ABR 2.5 vs. 37.2; RR=0.06, 95% CI: 0.04, 0.1) (Table 4.3). Similarly, there were fewer treated joint bleeds with Factor VIII prophylaxis compared to no prophylaxis (ABR 1.9 vs. 28.7; RR=0.06, 95% CI: 0.04, 0.12). We found no data on all bleeding events, treated spontaneous bleeds, and treated target joint bleeds. The mean adherence in the prophylaxis arm was 93%, and 88% of patients had

at least 80% adherence to factor VIII frequency and prescribed doses. The median prophylaxis dose in the trial was 26.6 IU/kg three times weekly.

Table 4.4 and 4.5 shows the results of the NMAs on the bleeding outcomes – treated bleeds and treated joint bleeds - of emicizumab versus factor VIII prophylaxis. Result of the NMA showed there was a non-significant lower rate of treated bleeds with emicizumab prophylaxis compared to factor VIII prophylaxis (RR=0.57, 95% CI: 0.22, 1.47). Similarly, NMA results showed a non-significant lower rate of treated joint bleeds on emicizumab prophylaxis compared to factor VIII prophylaxis (Table 4.5).

Table 4.3. Bleeding Outcomes Reported in HAVEN 3 and SPINART

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

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

Table 4.4. NMA Results of Annualized Treated Bleeds: Rate Ratio (95% Credible Interval)

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

Table 4.5. NMA Results of Annualized Treated Joint Bleeds: Rate Ratio (95% Credible Interval)

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

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

As described above, all patients in HAVEN 3 who had previously received prophylactic treatment with factor VIII were assigned to receive weekly emicizumab prophylaxis in the non-randomized arm.[33] Of the 63 patients who participated in this arm of the trial, 48 had participated in a prior non-interventional study, which was designed to collect data on bleeding events while patients were on factor VIII prophylaxis (median duration of follow up: 30.1 weeks). An intra-individual comparison was conducted among the 48 patients that participated in the non-interventional study by comparing each person's bleeding outcome during the prior non-interventional study while they were on factor VIII prophylaxis to their bleeding outcomes while on emicizumab in HAVEN 3. The analysis showed a 68% reduction in treated bleeds with emicizumab prophylaxis compared to factor VIII prophylaxis (ABR: 1.5 vs. 4.8, RR=0.32, 95% CI: 0.20, 0.51). There appeared to be a similar relative reduction in all bleeds (see Table 4.6). We found no data on the other bleeding outcomes.

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

Table 4.6. Emicizumab Prophylaxis versus Prior Factor VIII Prophylaxis in HAVEN 3 Trial

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

ABR: annualized bleeding rate, QW: Once weekly dosing (1.5 mg/kg)

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

†estimated (not reported)

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

In children less than 12 years old, we identified one open label, multicenter, non-comparative study (HOHOEMI) that assessed the rate of bleeding events in 13 Japanese children while on emicizumab

(Table 4.7).[36] The trial evaluated two maintenance doses of emicizumab (3 mg/kg every 2 weeks [Q2W] or 6 mg/kg every 4 weeks [Q4W]) in two cohorts. The ABR for "treated bleeds" in the Q2W and Q4W cohorts were 1.3 (95% CI: 0.6, 2.9) and 0.7 (95% CI: 0.2, 2.6), respectively. In 92% of the patients (n=12), individual ABRs for "treated bleeds" decreased or remained zero while on emicizumab compared to the pre-treatment period. However, details around how the bleeding events in the pre-treatment period was collected was not reported. Other related bleeding outcomes are presented in Table 4.7.

Table 4.7. Emicizumab Bleeding Outcomes Reported in HOHOEMI

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

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

Health-Related Quality of Life

Haem-A-QoL, a hemophilia-specific 46-item instrument, was used to assess health-related quality of life in HAVEN 3. At week 25, the observed difference between the emicizumab arms and the no prophylaxis arm in the Haem-A-QoL physical subscale score was not statistically significant (P=0.09).[33] The Haem-A-QoL total score was not reported. In the single arm HAVEN 4 trial, a mean change from baseline of 15.4 (95% CI 7.8, 22.4) was observed in the Haem-A-QoL physical subscale, which exceeded the minimum clinically-important difference (CID) of 10 points.[35]

We did not identify any data on Haem-A-QoL or any other quality of life measure for the before (Factor VIII prophylaxis) and after (emicizumab) comparison in HAVEN 3, or any data that allowed for indirect comparison on this outcome.

Emicizumab Preference Survey

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

In the before and after comparison done in HAVEN 3, 98% of patients favored emicizumab over factor VIII prophylaxis.[33] In HAVEN 4, all participants who were previously on factor VIII prophylaxis preferred emicizumab over their previous factor VIII treatment regimen. [35] Similarly, all caregivers reported a preference for emicizumab over the patient's previous factor VIII prophylaxis in the non-randomized open-label study conducted in Japanese children (HOHEMI).[36] Reasons for preference

for emicizumab were not provided in HAVEN 3 and HAVEN 4. However, in HOEHEMI, all caregivers indicated the lower frequency of treatment and easier route of administration as the major reasons for their preference for emicizumab.[36]

Mortality

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

Other Outcomes

We did not identify any studies that assessed the impact of prophylaxis with emicizumab on the other outcomes of interest, including pain, other patient-related outcomes (such as career choices, educational choices, recreational activities, anxiety, depression, overall well-being), outcomes for family and caregivers particularly of younger children with hemophilia A, or utilization of the health care system.

Harms of Emicizumab

About 85% of patients on emicizumab prophylaxis in HAVEN 3 experienced one or more adverse events. The most common treatment-related AE was injection site reaction, occurring in 25% of patients on emicizumab prophylaxis. Most of the AEs were reported to be mild. There was a total of 14 serious AEs in patients on emicizumab prophylaxis in HAVEN 3 (4 bleeding events, 1 cardiac disorder, 3 cases of infection, 3 musculoskeletal disorders, 1 psychiatric disorder, 1 trauma case, and 1 loosening of orthopedic device), none of which were considered by the investigators to be treatment-related. Similar patterns of AEs were observed in the two other emicizumab trials, with very few serious AEs and those that occurred were also deemed not to be related to emicizumab (Table 4.8). There were no reports of thrombotic microangiopathy, thromboembolism, hypersensitivity reactions, new development of factor VIII inhibitors, serious AEs related to co-exposure to emicizumab and factor VIII prophylaxis, or deaths in any of the trials.

Table 4.8. Emicizumab Adverse Events Reported in HAVEN 3, HAVEN 4 & HOHEMI

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

AE: adverse events

Trials of Valoctocogene Roxaparvovec

We identified two trials of valoctocogene roxaparvovec (one Phase I/II and one Phase III) that met our inclusion criteria, neither of which had a control arm (Table 4.9).

Key Trial of Valoctocogene Roxaparvovec

Phase I/II Trial (NCT02576795)

Evidence to inform our assessment of valoctocogene roxaparvovec were mainly derived from an open-label dose-escalation Phase I/II multiyear study conducted in 15 patients.[17,18,39,47,48] The trial enrolled male patients aged 18 years and older with severe hemophilia A without factor VIII inhibitors who had at least 150 days of previous exposure to factor VIII concentrate or cryoprecipitate. For patients who were receiving on-demand treatment, they had to have at least 12 bleeding events requiring factor VIII replacement treatment in the previous 12 months. Patients with pre-existing immunity to the adeno-associated virus type 5 (AAV5) capsid or those who showed any evidence of active infection or immunosuppressive disorder or tested positive for HIV were excluded.

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

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

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

The two patients enrolled in the lower dosed cohorts (cohort 1 & 2) did not achieve the pre-specified primary endpoint of factor VIII activity levels of 5 IU/dL at week 16 after gene transfer. At three years of follow up, both patients still had low factor VIII levels (< 1 IU/dL).[17,18] These lower doses are not anticipated to be used clinically and, as such, the lower dosed cohorts (cohort 1 and 2) are not described in the Clinical Benefits section of this review. However, safety data were supplemented with evidence from these low-dose cohorts.

Other Trials of Valoctocogene Roxaparvovec

Phase III GENEr8-1

We identified one ongoing open-label, single arm Phase III trial (GENEr8-1).[39,41] GENEr8-1 is evaluating high dose ($6x10^{13}$ vg/kg) valoctocogene roxaparvovec in patients 18 years and older with severe hemophilia A without factor VIII inhibitors who were on prophylactic factor VIII for at least 12 months prior to study entry. Patients with pre-existing immunity to the AAV5 capsid or those who showed any evidence of active infection or immunosuppressive disorder, including HIV infection, were excluded.

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

Table 4.9. Trials of Valoctocogene Roxaparvovec in Hemophilia A Without Inhibitors

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

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

Clinical Benefits of Valoctocogene Roxaparvovec

FVIII Activity Level

All seven participants in cohort 3 ($6x10^{13}$ vg/kg dose) and five out of the six participants in cohort 4 ($4x10^{13}$ vg/kg dose) achieved the pre-specified primary endpoint of factor VIII activity levels of 5 IU/dL or more at week 16.[18] At the end of year one, the mean factor VIII activity level in cohort 3 and cohort 4 as measured by chromogenic assay were 64 IU/dl (median: 60 IU/dl; range: 11-88 IU/dl), and 21 IU/dL (median: 23 IU/dl; range: <3-40 IU/dl), respectively. Using categories of hemophilia, all participants in cohort 3, except one who was in the mild hemophilic range, were in the non-hemophilic range at the end of year one. In cohort 4, five participants were in the mild hemophilic range, while one remained in the severe hemophilic range at the end of year one. Of note, the results of the factor VIII activity level using the less conservative one-stage assay showed levels that were approximately 1.6 times as high as those observed with the chromogenic assay (Year 1 cohort 3 [mean, 104 IU/dl; median, 89 IU/dl]; Year 1 cohort 4 [mean, 31 IU/dl; median, 32

IU/dl]). Over the course of the second year, factor VIII levels decreased in all cohort 3 participants and a majority of cohort 4 participants, resulting in a significant decline in the mean Factor VIII expression (chromogenic assay [Cohort 3: ↓44%; cohort 4: ↓29%]; one-stage assay [Cohort 3: ↓43%; cohort 4: ↓26%]).[17,18] The third and fourth year follow up results showed continued decline in factor VIII expression, albeit slower (Table 4.10 and 4.11). [17,18,47,48] For cohort 3 ($6x10^{13}$ vg/kg dose) participants, the year four data on factor VIII activity as measured by the more conservative chromogenic assay showed one participant back in the severe hemophilic range, four participants in the mild hemophilic range, one participant in the moderate hemophilic range, while one participant remained in the non-hemophilic range.[47] The one-stage assay measurement placed five participants in the mild hemophilic range, and the remaining two in the non-hemophilic range at year four.[47]

Table 4.10. Valoctocogene Roxaparvovec. Factor VIII Activity Over 4 Years in Cohort 3 ($6x10^{13}$ vg/kg) of Phase I/II Study

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

*CS: Chromogenic.

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

% Δ: percent change

Table 4.11. Valoctocogene Roxaparvovec. Factor VIII Activity Over 3 Years in Cohort 4 ($4x10^{13}$ vg/kg) of Phase I/II Study

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

Table 4.12. Valoctocogene Roxaparvovec. Hemophilic Range in Phase I/II study

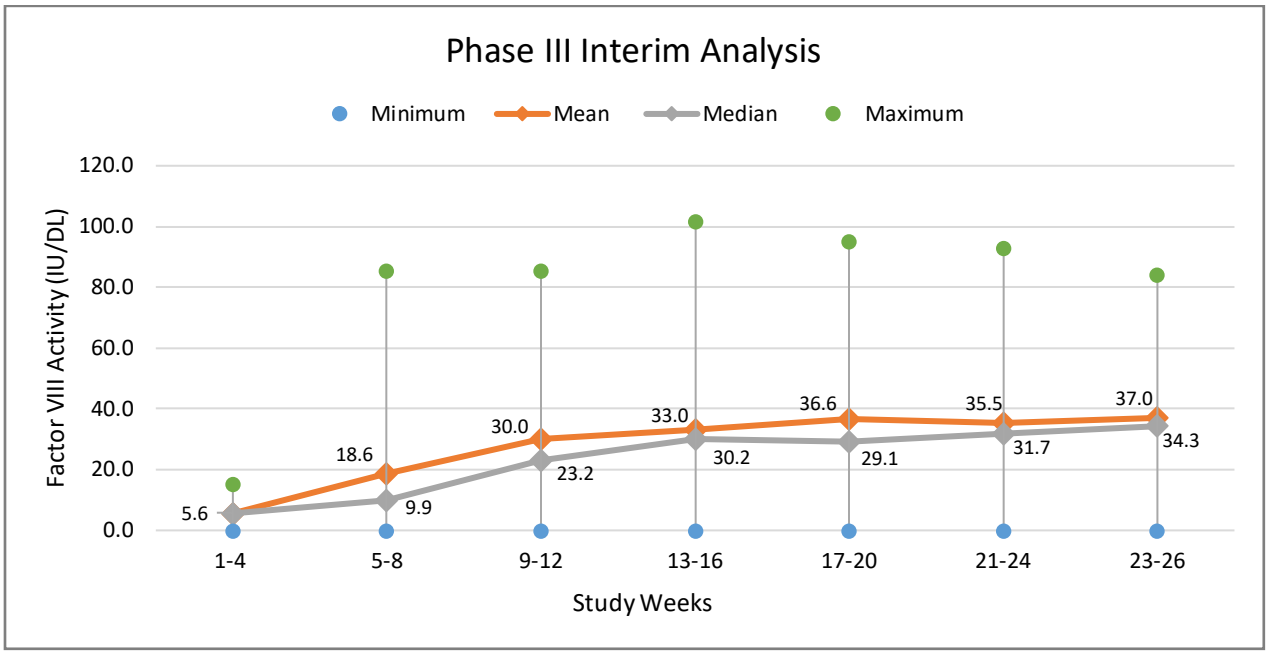
Cohort 3 ($6x10^{13}$ vg/kg); n=7	Hemophilic range as measured by CS over 4 years				Year 4 range as measured by one-stage assay*
	Year 1 (CS)	Year 2 (CS)	Year 3 (CS)	Year 4 (CS)	
Non-hemophilic (>40 IU/dl)	6	2	1	1	2
Mild hemophilia (>5 IU/dl)	0	4	5	4	4
Moderate hemophilia (1-5 IU/dl)	1	1	1	1	0
Severe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

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

Of the 16 patients who had reached 26 weeks at the time of the interim analysis in the Phase III trial of $6x10^{13}$ vg/kg valoctocogene roxaparvovec (GENEr8-1), seven had achieved the pre-specified factor VIII levels of 40 IU/dl or greater.[39] Figure 4.1 presents the progression of factor VIII activity as measured by chromogenic assay in the 16 participants from week 1 to week 26. At week 1-4, the mean factor VIII activity level was 5.6 IU/dl (median: 5.6 IU/dl; range:<1-15.1). By week 16, the mean factor VIII activity had risen to 33 IU/dl (median: 30 IU/dl; range: <1-100 IU/dl), after which

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

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



Rates of Bleeding Events

Table 4.13. presents data on the mean ABR for 'treated bleeds' for up to four years of follow up in the Phase I/II valoctocogene roxaparvovec trial.[17,18] Data were presented only for the participants who were on factor VIII prophylaxis in the year before the study (6 out of 7 patients in cohort 3 and all 6 patients in cohort 4).

In cohort 3 ($6x10^{13}$ vg/kg dose), the mean ABR for 'treated bleeds' dropped from a baseline of 16.3 events per year (SD:15.7) to a cumulative mean of 0.8 per year, after four years of follow up, representing a 95% reduction.[17,18,47,48] At baseline, only one participant in cohort 3 who had been on factor VIII prophylaxis had zero bleeding events. Following the administration of valoctocogene roxaparvovec, five out of the seven participants in cohort 3 had zero bleeding events in year one of the study; and six out of seven participants had zero bleeding events in year two to year four of the study (Table 4.13). In addition, all participants had full resolution of bleeding in target joints by year two, with continued absence of target joint bleeds in all participants in year 3 (year 4 data not available).

Patients in cohort 4 ($4x10^{13}$ vg/kg dose) also had a large reduction (93%) in the mean ABR for 'treated bleeds' from a baseline of 12.2 (SD:15.4) to a cumulative mean of 0.9 after three years of follow up.[17,18,47,48] In cohort 4, 67% of participants had zero bleeding events at the end of year two

and year three, compared to 16% at baseline (Table 4.13). In addition, five of six participants had full resolution of bleeding in target joints by year two, with continued absence of target joint bleeds in the five participants in year three.

In the Phase III trial of $6x10^{13}$ vg/kg valoctocogene roxaparvovec (GENEr8-1), the mean ABR for 'treated bleeds' for the 16 patients who had reached 26 weeks at the time of the interim analysis was 1.5, representing an 86% reduction from a mean of 9.9 events per year. [39]

Table 4.13. Valoctocogene Roxaparvovec. Bleeding Events in the Phase I/II Study

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

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

Factor VIII Use

Data on mean annualized factor VIII use for up to four years of follow up in the Phase I/II trial of valoctocogene roxaparvovec are presented in Table 4.14. In the year before the study, the mean annualized number of factor VIII infusions per year was 136.7 (SD: 22.4) in cohort 3, and 146.5 (SD: 41.6) in cohort 4.[17,18,47,48] At four years post-administration of valoctocogene roxaparvovec, there was a 96% overall reduction in annualized factor VIII use to a cumulative mean of 5.3 infusions per year. [17,18,47,48] Similarly, the mean annualized rate of factor VIII use in cohort 4 was reduced by 96% to a cumulative mean of 5.7 after three years of follow up.

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

Table 4.14. Valoctocogene Roxaparvovec. Mean Factor VIII use in the Phase I/II Study

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

Yr: year
N: number
NA: not applicable

Health-Related Quality of Life

Haem-A-QoL, a hemophilia-specific 46-item instrument, was used to assess the health-related quality of life in the Phase I/II study. In cohort 3, a steady increase was seen in the Haem-A-QoL total score of participants over four years of follow-up (Table 4.15).[48] The mean change from baseline observed over the four years of follow-up matched or exceeded the minimum clinically important difference (CID) of 10 points. [48]

In cohort 4, participants saw the greatest improvement in Haem-A-QoL total score at year three (difference of 2.1), however the improvement remained less than the minimum CID of 10 points

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

Table 4.15. Valoctocogene Roxaparvovec. Mean Haem-A-QoL Total Score in the Phase I/II Study

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

N: number
Δ: change

Mortality

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

Other Outcomes

We did not identify any studies that assessed the impact of valoctocogene roxaparvovec on the other outcomes of interest, including pain, other patient-related outcomes (such as career choices, educational choices, recreational activities, anxiety, depression, overall well-being), outcomes for family and caregivers, or utilization of the health care system.

Harms of Valoctocogene Roxaparvovec

All participants in the Phase I/II trial of valoctocogene roxaparvovec experienced one or more adverse events. [17,18] The most common treatment-related AE was elevation of the alanine aminotransferase (ALT) level, occurring in 86% of patients in cohort 3 and 67% of patients in cohort 4. Participants in the lower dosed cohorts (cohort 1 and 2) did not experience elevations in ALT levels. None of the enzyme elevations were accompanied by markers of cholestasis or were associated with symptoms suggestive of liver dysfunction. As noted above, participants in cohort 3 received glucocorticoid prophylactically in response to the enzyme elevation noted in the first patient in the cohort, while participants in cohort 4 were treated with glucocorticoid only if required clinically (due to a protocol amendment). Serious adverse events occurred in three participants over three years of follow up. Two of the three had events considered by the investigators to be unrelated to treatment (elective total knee replacements surgery for preexisting hemophilic arthropathies). The third patient presented with transient infusion-associated reactions (myalgia, headache, and grade 2 fever) within 24 hours after administration of valoctocogene roxaparvovec; all symptoms resolved within 48 hours after treatment with acetaminophen. Two new serious adverse events considered by the investigators to be unrelated to treatment (details not reported) were reported in the newly released data on year four. [48]

Similar to the Phase I/II trial, the most common treatment-related AE observed in the ongoing Phase III trial as of the data cutoff date was elevation of the ALT level (17 participants, 77%).[39] Other common adverse events observed were nausea (50%), headache (46%), fatigue (41%), and aspartate aminotransferase (AST) elevation (36%). Three participants reported serious adverse events, two of which were judged to be treatment related (details not reported).[39]

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

Table 4.16. Valoctocogene Roxaparvovec. Adverse Events Reported in Phase I/II & Phase III Studies

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

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

Uncertainty and Controversies

Use of emicizumab in very young children likely affects the rate of development of inhibitors to factor VIII since it both precludes the need for prophylaxis with factor VIII, thus reducing exposure, but may increase the likelihood that initial or early exposure to factor VIII will involve higher quantities of factor VIII when it is administered to treat bleeding. As discussed in ICER's prior report, the development of inhibitors has very important implications for management, costs, and quality of life. There is no high-quality evidence assessing how emicizumab used in this way affects the rate of inhibitor development and we heard expert opinion that it could increase or decrease the risk of developing factor inhibitors. A randomized clinical trial is comparing emicizumab to factor VIII (Eloctate) in the prevention of inhibitors (see Appendix C).[49]

The evidence comparing emicizumab with Factor VIII prophylaxis is indirect and there are wide confidence intervals around the point estimates of effect.

We chose to compare emicizumab with factor VIII prophylaxis using results of each from randomized trials. If reductions in adherence outside of trials are not similar for the two therapies this could incorrectly characterize the relative benefits of the therapies in the real world. Emicizumab prophylaxis is substantially less burdensome than factor VIII prophylaxis, and so real world adherence is likely to be more similar to clinical trial adherence with emicizumab than with factor VIII.

The evidence on valoctocogene roxaparvovec has multiple limitations creating uncertainties:

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

The manufacturer of valoctocogene roxaparvovec has suggested that the low bleeding rates seen even as factor VIII levels decline imply that the factor VIII produced by gene therapy may be more biologically active than the factor VIII in patients with mild or moderate hemophilia since mild and moderate hemophilia are typically the result of a mutation that may alter the functional capacity of factor VIII as well as its expression. This appears to be a *post hoc* explanation for results based on a small number of data points.

Valoctocogene roxaparvovec targets hepatocytes rather than endothelial cells, the liver cells that normally produce factor VIII. It is uncertain whether over the long term this could result in chronic liver inflammation or other liver disorders, or if expression could wane in patients with chronic HCV infection whose fibrosis progresses.[50] Concerns have also been expressed in the hemophilia community that low level inflammation related to transfection with AAV5 could lead to long-term liver damage as has been seen with chronic hepatitis C infection and that these harms might take many years to become apparent.

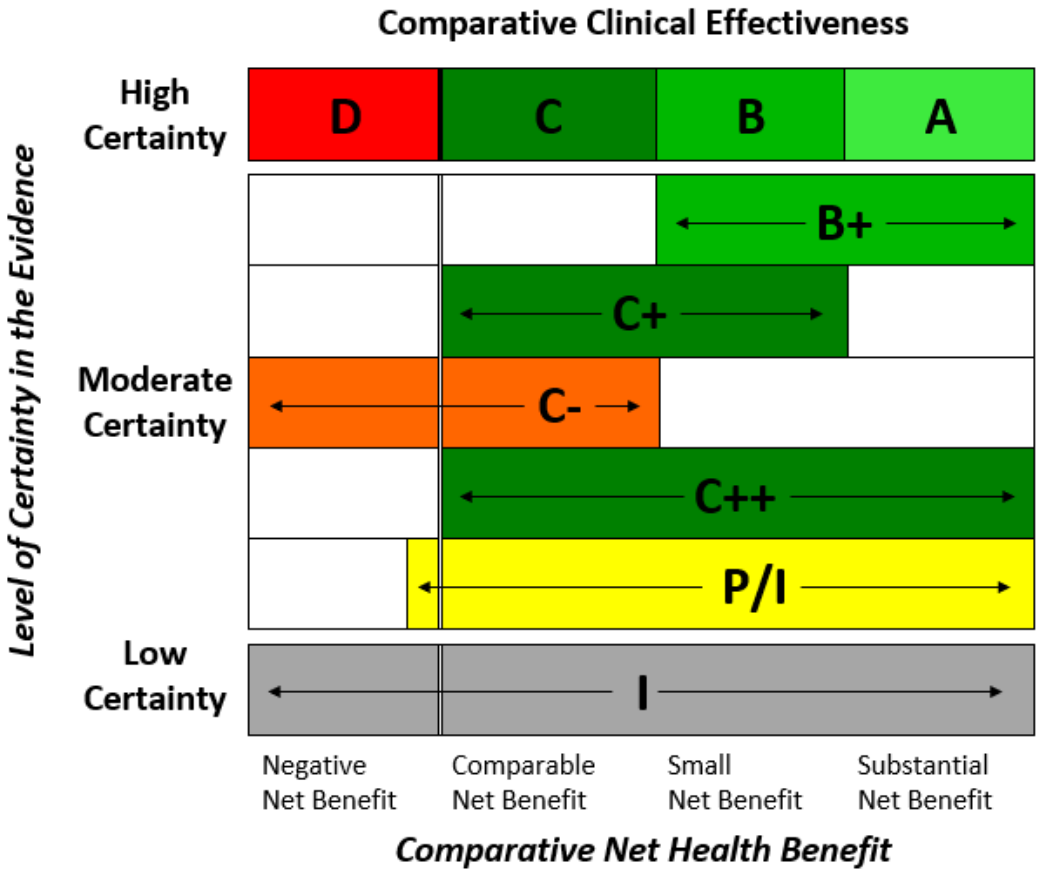
Patients who are treated with valoctocogene roxaparvovec typically develop antibodies to AAV5. This may prevent retreatment with valoctocogene roxaparvovec or treatment with another therapy using AAV5, but it is also possible that in the future it will be possible to overcome antibody development or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

Heterogeneity and Subgroups

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

4.4 Summary and Comment

Figure 4.2. ICER Evidence Rating Matrix



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

Table 4.17. ICER Evidence Ratings

Interventions	ICER Evidence Rating
Emicizumab Versus Factor VIII Prophylaxis	B+
Valoctocogene Roxaparvovec Versus Factor VIII Prophylaxis	P/I
Emicizumab Versus Valoctocogene Roxaparvovec	I

Emicizumab Compared with Factor VIII Prophylaxis

Prophylaxis with either emicizumab or factor VIII is far superior to no prophylaxis in patients with severe hemophilia A. Emicizumab appears to have lower bleeding rates (of all types) compared with factor VIII, perhaps because it avoids the peak and trough levels that occur with intermittent factor VIII administration. Given the lack of head-to-head trials, the degree of reduction in bleeding with emicizumab is uncertain. Also, the long-term effects on joint disease are unknown, both in patients who initiate emicizumab as young children and in adults who initiate it and already have established joint disease.

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

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

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

Valoctocogene Roxaparvovec Compared with Factor VIII Prophylaxis

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

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

Liver inflammation can occur acutely with valoctocogene roxaparvovec, but this has typically not been a severe problem. More concerning is the possibility that antibodies to AAV5 could interfere

with other treatments including other, perhaps more durable, gene therapies for hemophilia A and treatments or vaccines for conditions such as Covid-19.[51] An additional concern is whether therapy with valoctocogene roxaparvovec could lead to chronic liver inflammation, perhaps because the transfected cells are not the cells that normally produce factor VIII.

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

Valoctocogene Roxaparvovec Compared with Emicizumab

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

5. Long-Term Cost Effectiveness

5.1 Overview

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

Our approach is based on accomplishing two primary objectives, using Markov models. The first was to estimate the cost effectiveness of valoctocogene roxaparvovec compared to prophylaxis with factor VIII preparations in adult patients with severe hemophilia A without inhibitors to factor VIII. The analysis for this first primary aim followed the ICER ultra-rare disease framework and includes a health care sector perspective (i.e., focus on direct medical care costs only) and a societal perspective as co-base cases, each using a lifetime time horizon. As valoctocogene roxaparvovec is a one-time gene therapy for hemophilia A, this analysis was also conducted using ICER's High-Impact Single and Short-Term Therapies (SST) framework.

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

5.2 Methods

We developed a *de novo* decision analytic model for patients with hemophilia A without inhibitors to factor VIII (hereafter referred to as without inhibitors), informed by key clinical trials and prior relevant economic models. The model was used to conduct the evaluation of valoctocogene roxaparvovec in adult patients with severe hemophilia A without inhibitors, where there were dual base-case analyses following ICER's ultra-rare disease framework, and the evaluation of emicizumab in patients with hemophilia A without inhibitors eligible for factor VIII prophylaxis, where that base case took a health care sector perspective. In each case, costs and outcomes were discounted at 3% per year.

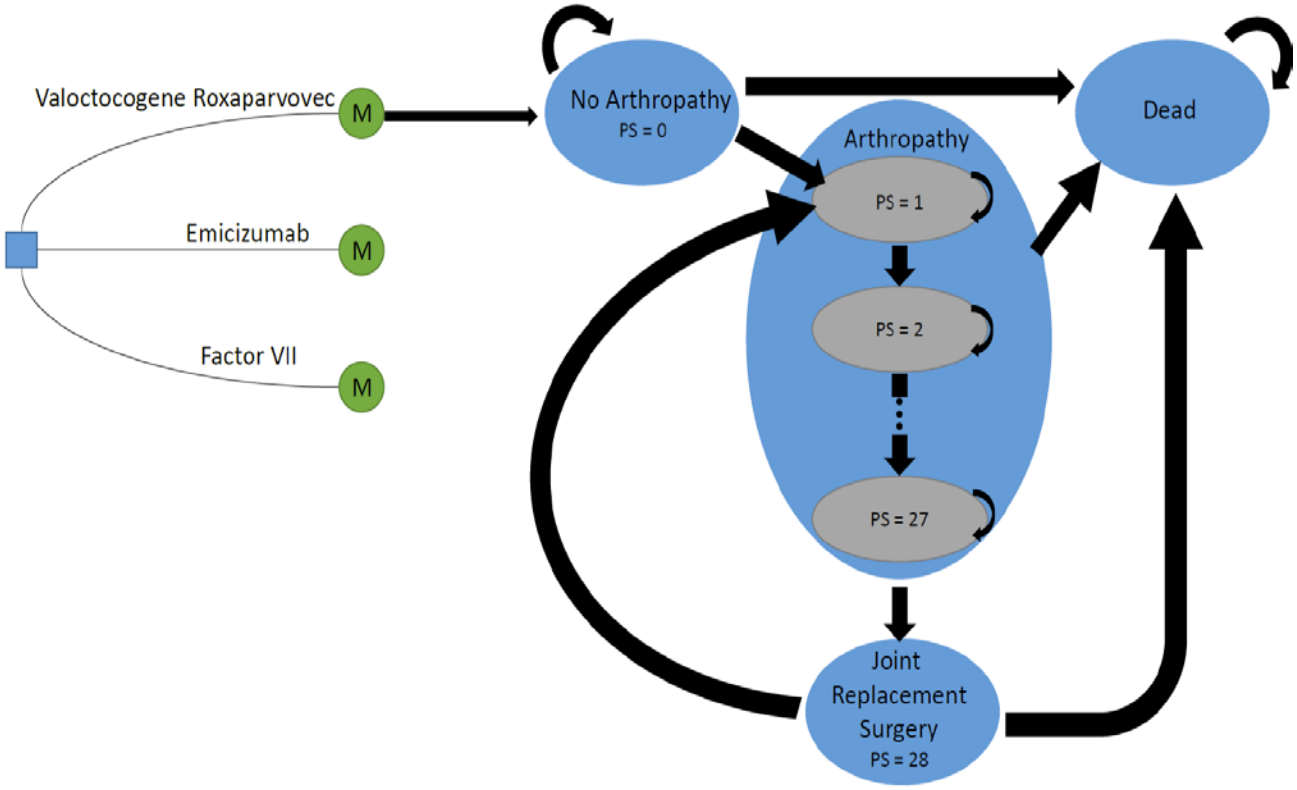
The first version of the model centered on an intention-to-treat analysis, with a hypothetical cohort of adult patients with severe hemophilia A without inhibitors being treated with valoctocogene roxaparvovec, or factor VIII prophylaxis. The second version of the model focused on an intention-to-treat analysis, with a hypothetical cohort of patients with hemophilia A without inhibitors eligible for prophylaxis for factor VIII being treated with emicizumab or factor VIII. The cycle length in both versions of the model was 6 months, based on the literature related to bleed rates and subsequent

long-term development of joint damage from target joint bleeds as tracked by Pettersson scores (PS). The model versions each used a lifetime time horizon for the base case. The models were developed in Excel 2016.

Model Structure

Given the importance of acute bleeds, as well as the long-term joint damage caused by joint bleeds that lead to arthropathy and the potential need for joint replacement surgery, the model was structured using tunnel states corresponding to PS that range from 0-28. Upon reaching a PS of 28, the base case model assumed patients have joint replacement surgery and return to a PS of 1. Transitions through the PS states in the models were based on the expected frequency of joint bleeds associated with the treatments and subsequent expected increases in the PS.[52] Patients also had age-varying mortality rates that are not related to PS. Patients with a PS of 0 will be viewed as having "no joints with arthropathy," patients with a PS of 1-27 will be viewed as having "at least one joint with arthropathy," and patients with a PS of 28 will be viewed as "requiring surgery." Hence, while incorporating the tunnel states based on progression through PS, the model may be viewed as having four general health states: no arthropathy, arthropathy, joint replacement surgery, and death. In each cycle, the expected number of bleeds across treatments were modeled along with related costs and impacts on patient utilities (Figure 5.1). Patients remained in the model until they die. All patients could transition to death from all causes from any of the alive health states.

Figure 5.1. Markov Model Schematic for Model Versions 1 and 2



M: Markov node, PS: Pettersson score

Costs and utilities will be assigned in each cycle based on bleeds as well as on the level of arthropathy in the particular health states.

Target Population

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

In the base-case analysis for valoctocogene roxaparvovec, version 1, patients enter the model at the age of 18 and start in the average PS for that age, based on average PS of 18 year old's reported in the literature.[52] In the base-case analysis for emicizumab, version 2, patients enter the model at age 1 year with a PS of 0.

Treatment Strategies

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

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

Comparators

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

Key Model Characteristics and Assumptions

Below is a list of key model choices:

- Bleed rates determine transition rates across PS, costs, and utilities in the model.
- Relative bleed rates for emicizumab compared to factor VIII were derived from an ICER NMA of available trials, and are applied to bleeding rates seen in the HAVEN 3 trial to get the absolute rates used in the models.
- Bleed rates for valoctocogene roxaparvovec in the first version of the 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.[53] At projected factor levels below 5%, 5% of patients are assumed to switch to emicizumab prophylaxis. At projected factor levels below 1%, all patients will be assumed to switch to prophylaxis with factor VIII, or to prophylaxis with emicizumab if it dominates factor VIII at typical doses in version 2.
- 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 total joint bleeds from data on treated bleeds.
- The model structure was based around the PS. This allows for longer-term cycles while still accounting for bleeds each year as well as the development of arthropathy and the possibility of requiring surgery.
- The model used 6-month cycles. This was the longest standard cycle that allowed for reasonable transition rates between PS counts each cycle, given the expected bleeding rates possible in the model.

- Survival was weighted by health state utilities derived from the published literature.[54-58] The model includes separate utilities for different types of bleed events, varying baseline utility by age and arthropathy, and utility associated with requiring surgery.
- The model included all direct treatment costs associated with each individual regimen, including drug acquisition costs and non-pharmacy costs (including all medical expenses associated with bleeds).
- All costs prior to 2019 were adjusted for inflation following methods outlined in the ICER reference case so that all cost inputs and outputs in the model reflect 2019 US dollars.[59,60]

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

Table 5.1. Key Model Assumptions

Assumption	Rationale
Total bleeds relative to treated bleeds are modeled based on the emicizumab arm of the HAVEN 3 trial.[33] Joint bleeds were assumed to be the same percentage of all bleeds for each comparator in base case analyses using a simple average of rates of total joint bleeds to all bleeds seen in the various arms of the HAVEN 3 trial (provided by Genentech) and the proportion seen in the POTTER trial (resulting in 0.66 as the proportion used).[61] [33]	Treated bleeds are most commonly measured, but total joint bleeds have been shown to impact the PS.[61,62] The POTTER trial offered the only published account of all bleeds and all joint bleeds associated with hemophilia A but data were made available from HAVEN 3 as well. There is no clinical reason to believe that the proportion of bleeds that are joint bleeds, or what proportion of all bleeds would be treated, would vary by treatment, and provided data do not suggest any such difference.
Annual bleed rates are equivalent regardless of the degree of arthropathy.	Data on the relative occurrence of bleed events pre- and post-arthropathy are limited. Increasing bleed rates due to arthropathy are explored in a scenario analysis.
Pettersson scores (representing joint arthropathy development) increase as a function of joint bleeds (treated and/or untreated) over time at different rates for patients over and under the age of 25.	Pettersson scores have most recently been reported to increase by one point for every 36.52 joint bleeds (treated and/or untreated) in patients under 25 and by one for every 6.52 joint bleeds for patients over 25.[62]
All patients were assumed to be male, and patient weight and background mortality was based on US male population averages.	Hemophilia is an X-linked recessive disease primarily affecting males. Females with hemophilia A typically have less severe disease. We assume that prophylaxis of hemophilia will not substantially impact weight or mortality.
The utilities associated with a bleed are applied for two days. After two days we assume the bleed state utility is an average of the no bleed and bleed values for the remainder of a week to reflect that the impact of the bleed on utility lingers after the bleeding stops.	The duration of a bleed is estimated to be two days. However, the impact of a bleed likely lingers beyond bleed duration and treatment time. The number of days per week for bleed utilities is varied in a scenario analysis.
Bleed disutilities were derived from patients with inhibitors as opposed to patients without inhibitors and hence the bleed disutility was assumed to be the same for those without inhibitors as seen in those with inhibitors.	The bleed disutilities in the population with inhibitors could potentially be greater than those without inhibitors. Thus, the treatment effect of emicizumab and valoctocogene roxaparvovec may be slightly overestimated. Sensitivity analyses around these bleed utilities were assessed
Cost per treated bleed event is the same for all comparators.	We have not seen evidence to support different on-demand treatment costs for patients on different forms of prophylaxis.

Model Inputs

Clinical Inputs

Bleed Rates

The rates of bleeds seen in Group B of the Haven 3 trial were used for emicizumab. Relative rates of treated bleeds and treated joint bleeds from the combined regimen ICER NMA involving emicizumab and factor VIII treatments combined with the treated bleeds and treated joint bleeds for emicizumab were used to determine the rates of treated bleeds and treated joint bleeds for factor VIII. The ratio of treated target joint bleeds to treated joint bleeds seen in Group B of the HAVEN 3 trial was used to estimate treated target joint bleeds from the number of treated joint bleeds for Factor VIII. In addition, the ratio of all bleeds to treated bleeds seen in Group B of the HAVEN 3 trial was used to estimate total bleeds for factor VIII. An average of the ratios of all bleeds that were joint bleeds in all the arms of the HAVEN 3 as well as that seen in the POTTER trial were used to estimate total joint bleeds from treated bleeds for emicizumab and factor VIII.[33,61]

Treated bleed rates for valoctocogene roxaparvovec were modeled based on available evidence of treated joint bleed rates across factor levels seen in moderate and mild hemophilia patients by den Uijl et al.[53] To estimate treated joint bleed rates, median one-stage factor VIII levels of high dose patients from BioMarin were combined with estimated rates of treated joint bleeds by factor level in den Uijl et al. In addition, to balance these estimates with lower than usual bleed rates seen in the trials, patients with factor levels above 50 were assumed to have zero bleeds, and patients with factor levels between 1 and 3 percent were assigned the bleed level of those with 3%. Further, we averaged across the tail of the bleed rates for factor levels of 11 and up and assigned that to all those between 50 and 11 and made a slight adjustment (i.e. changed from 0.78 to 0.80) to a non-monotonic portion of the relationship between factor levels and bleeds at factor levels less than 11 after digitizing figure 2 from den Uijl et al.[53] Declines across time in average patient factor levels available at 26 weeks for all patients were projected forward based on proportional declines seen in available data covering years 1-4. The projections also used the average percent declines seen between years 2 and 3 and years 3 and 4 to project year 5 and beyond. Once patients were projected to be at factor levels below 5% (cycle 16), 5% of the patients were assumed to switch treatment, and then once the patients were projected to be at less than 1% (cycle 25), all patients were assumed to switch treatment. Finally, for the first cycle of treatment for valoctocogene roxaparvovec, we assumed patients would experience 3 months with a bleed rate equal to that of factor VIII prophylaxis, and 3 months with a bleed rate of zero.

Estimates of the other types of bleeds for valoctocogene roxaparvovec were then based on the same relative proportions of bleeds used for factor VIII described above. For example, we used the ratio of total treated bleeds to total treated joint bleeds as well as the ratio of total bleeds to total

treated bleeds from HAVEN 3 and assumed as described above for the other treatments that 0.66 of all bleeds would be joint bleeds.

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

Table 5.2. Annual Bleed Rates

Drug	All Bleeds	All Joint Bleeds	Treated Non Target Joint Bleeds	Treated Target Joint Bleeds
Factor VIII	4.56	3.01	1.09	1.19
Emicizumab	2.60	1.72	0.60	0.70
Valoctocogene Roxaparvovec Year 2	0.45	0.30	0.10	0.12
Valoctocogene Roxaparvovec Year 10	7.05	4.65	1.63	1.90
Valoctocogene Roxaparvovec Year 13	2.60	1.72	0.60	0.70

Transition Probabilities

Transition probabilities between the PS-based health states were based on expected annual joint bleed rates and a literature-based assumption that on average 36.52 joint bleeds result in an increase of the PS by one for patients under age 25 and 6.52 joint bleeds result in a one-point PS increase in patients aged 25 years or more.[62] Hence, the annual number of joint bleeds divided by 36.52 and subsequently by 6.52 as patients reach 25 years old can be thought of as an annual transition rate to the next higher PS. Consequently, half the annual bleed rate divided by 36.52 and then 6.52 corresponds to the transition rate using 6-month time cycles. Bleeding rates in the HAVEN 3 trial were only reported for those at or above the age of 12. For the child model, bleed rates from HAVEN 3 are proportionally lowered based on the observed bleed rates for those aged 12 and older versus those under age 12 in the HAVEN 1 trial. When the child reaches 12 years old, bleed rates from the HAVEN 3 trial are used. Following surgery, all patients (minus those expected to die of all causes) are assumed to return to the arthropathy health state with a PS of 1.

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

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

Drug	Age < 12	12 ≤ Age < 25	Age ≥ 25
Factor VIII	0.011	0.022	0.118
Emicizumab	0.006	0.016	0.085
Valoctocogene Roxaparvovec Year 1	N/A	0.010	0.056
Valoctocogene Roxaparvovec Year 2	N/A	0.008	0.042

N/A: not available

Discontinuation

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

Mortality

Age-specific all-cause mortality was sourced from the CDC life tables for males which are representative of the male population in the US.[63] Prophylaxis for hemophilia A in patients without inhibitors has not been demonstrated to decrease mortality,[64] and the mortality rates seen over recent decades may not apply now that there are effective therapies for HIV and hepatitis C and new cases related to factor VIII contamination are unlikely to occur. As such, there is little evidence to suggest a differential mortality effect across options for prophylaxis.

Serious Adverse Events

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

Heterogeneity and Subgroups

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

Utilities

Health state utilities were derived from published literature sources and will be applied to the relevant health states. Baseline utility was taken from results of EQ-5D utilities based on responses from hemophilia patients broken out by age and degree of arthropathy, found in Ohara et al. (Table 5.4)[65] All of the disutilities associated with bleeds and with surgery used in the model were measured in patients with hemophilia A using the EQ-5D.[54,55,57,65,66] We used the same health state

utility values across treatments evaluated in the model. Utility in the surgery state was modelled using one month of having a time-tradeoff utility found in a general hip replacement pre-surgery patient group reported in the literature in 1993 (0.32), and 5 months with utility corresponding to a PS of 1-27 and the age of the patient getting surgery in the model.[57,66]

Table 5.4. Health State Utilities

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

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

Disutilities by bleed type were estimated based on differences in utilities reported during bleeds versus when having no bleeds, measured in patients with hemophilia A with inhibitors.[54,55] As stated above, bleed-associated disutilities for treated target joint bleeds and treated non-target joint bleeds were applied in full for two days, followed by an average of "No Bleed" and "Bleed" utilities for five days (Table 5.5).[54] In reality, bleed duration will vary depending on severity of the bleed, time to treatment, and other variables including location, so we have varied this assumption in a scenario analysis.

Table 5.5. Bleed-Related Disutilities

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

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

Economic Inputs

Drug utilization for factor VIII was based on a market basket approach using proportions of different types of factor VIII treatments seen in recent market basket data provided by the American Thrombosis and Hemostasis Networks (ATHN), representative treatments of each type, and typical doses for those products. Specifically, Advate® was selected to represent standard half-life treatment, used by 71.18 % of the patients, and Eloctate® was selected to represent extended half-life treatment, used by 28.82% of patients. To estimate utilization during bleeds, given input from clinical experts that most patients treat bleeds with the same drug they are using for prophylaxis, the same market basket will be used but with doses for each drug consistent with treating bleeds.

Utilization of emicizumab was assumed to be the same as seen in HAVEN 3.[33] Utilization for valoctocogene roxaparvovec was the highest dose seen in the available trials, as that dose was associated with the largest treatment effects across time (Table 5.6).

Use of standard half-life factor VIII prophylaxis was based on the dose seen in the trial from which the efficacy estimates were derived, and the use of extended half-life was estimated based on clinical opinion of equivalence as well as with the corresponding drug label for Eloctate.[33,67,68] Dosing of these drugs varies by weight. Patient weight by age was modeled based on average weight by age for males in the US. Specifically factor VIII prophylaxis with Advate and Eloctate used doses of 80 IU/kg every week and 78 IU/kg every week, respectively. In addition, because we recognized that these doses were lower than the most recent doses used in the US from the above analysis from ATHN, we conducted scenario threshold analysis. This scenario analysis used doses of 118.2 IU/kg for Advate and 111.2 IU/kg for Eloctate and the same market basket proportions to project treatment costs and then give associated efficacy levels in terms of bleed rates that would have to be achieved for factor VIII to make the use of emicizumab in the second version of the model not cost effective at various threshold levels. (Given the base case results below, valoctocogene roxaparvovec was not included in this analysis.)

For valoctocogene roxaparvovec, a dose of $6x10^{13}$ vg/kg was used which has been found to have the best efficacy in available trials. For emicizumab, 3 mg/kg every week for the first month and then 3 mg/kg every other week after the first month was used which is consistent with the best efficacy seen in the Haven 3 trial.[33] A lifetime treatment duration is assumed in each version of the model.

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

Table 5.6. Treatment Regimen Recommended Dosage

Generic name	Drug A	Drug B	Drug C	Drug C
Brand Name	Hemlibra®	Roctavian™	Advate®	Eloctate®
Generic Name	Emicizumab	Valoctocogene roxaparvovec	Antihemophilic factor (recombinant)	Antihemophilic factor (recombinant), Fc fusion protein
Manufacturer	Genentech	BioMarin	Baxter	Biogen
Route of Administration	subcutaneous	IV	IV	IV
Dosing	3mg/kg every week for the first month and then 3 mg/kg every 2 weeks after	$6x10^{13}$ vg/kg	80 IU/kg every week	78 IU/kg every week

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

Drug Costs

As valoctocogene roxaparvovec has not been approved, no WAC or net price estimates are available. We therefore conducted the base-case analysis using a placeholder price of $2,500,000, based on statements from the manufacturer indicating consideration of prices of around $2 million to $3 million per treatment.[69] In the absence of data on usual discounts for gene therapy, we assumed no discounting and used this placeholder for the net price of this treatment. For the other drugs in this analysis, we derived net prices from average sales prices (ASP) to calculate treatment-related health care costs, as we did not have other data on net prices that included discounts/rebates for these agents.[70] Based on the regimen dosage specified in Table 2.6 and available formulations for each drug, the model will utilize the lowest-cost combination of vials for each regimen. Further, available prices were adjusted by removing the portion of costs associated with a furnishing fee and add on costs. This involved a 45 cents reduction per mg and a six percent deduction for emicizumab and a 23 cent reduction per IU for the factor VIII products along with a six percent deduction (see Table 5.7).

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

Drug	WAC per Dose	Discount from WAC*	Add-On Discount	Net Price per Dose†	Net Price per Year‡
Valoctocogene roxaparvovec (Roctavian™)	$2,500,000#	--	0%	$2,500,000#	Not applicable
Emicizumab§ (Hemlibra®)	$100.19/mg	4.7%	6%	$89.33/mg	$569,105
Antihemophilic Factor (recombinant) (Advate®)	$1.69/IU	18.6%	6%	$1.08/IU	$367,201
Antihemophilic Factor (recombinant), Fc fusion protein (Eloctate®)	$2.23/IU	3.2%	6%	$1.82/IU	$601,852

*Calculated from WAC and ASP

†Net price from July 2020 ASP Pricing File, available at: https://www.cms.gov/medicare/medicare-part-b-drug-average-sales-price/2020-asp-drug-pricing-files, accessed June 30, 2020. From those numbers .23/IU for each factor VIII drug and 0.45 per mg for emicizumab was taken off along with 6% of the remaining costs to adjust for the portion of costs made up by a furnishing fee that would not generally apply.

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

§Maintenance dose

#Placeholder price for valoctocogene roxaparvovec

Treatment Cost Per Bleed

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

Non-Drug Costs

Health State Costs

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

on prophylaxis. However, the study found statistically significantly lower costs for patients under the age of 18 on prophylaxis and the estimated reduction was included for those patients in the model.[71]

Table 5.8. Non-Drug Costs per Bleed by Age

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

Added Cost of Arthropathy

In addition to the per-bleed costs, published findings of increased utilization associated with arthropathy were incorporated into the model. Specifically, reported differences in annual use of outpatient physician visits, outpatient nurse visits, as well as joint-related tests including X-ray and magnetic resonance imaging were used along with CMS physician fee schedule costs for 2018, inflated to 2019 (see Table 5.9).[72,73]

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

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

*The cost of surgery was derived from Earnshaw et al., which reported a surgery cost of $44,717.17 when inflated to 2019 dollars.[74]

Societal Costs

Costs associated with lost time from work for patients and caregivers were estimated based on a burden of illness analysis by Zhou et al.[75] The costs were inflated from 2011 to 2019 by using the total compensation per hour for civilian workers from the Bureau of Labor Statistics. The calculated cost per treated bleed was $1,162.28.

Equal Value of Life Years Gained

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

Sensitivity Analyses

We ran one-way sensitivity analyses to identify the key drivers of model outcomes, using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges for each input described in the model inputs section above. Probabilistic sensitivity analyses were also performed by jointly varying all model parameters over 10,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results. The selected distributions for the inputs can be found in Table E2 in Appendix E. From the probabilistic sensitivity analyses we generated acceptability curves showing the percent of simulations where the treatment in question is deemed cost effective relative to the comparator at various levels of willingness to pay for QALYs.

Scenario Analyses

The scenario analyses included the following:

- Extending duration of disutility from bleeds to 7 full days from 2 full days and 5 half days.
- Doubling the bleed rates for patients with arthropathy across all treatments.
- Including societal costs for emicizumab versus factor VIII prophylaxis (version 2)
- A scenario where patients begin valoctocogene roxaparvovec 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 13

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

In addition, as described above, we conducted scenario analyses in both versions of the model using higher and more representative doses of factor VIII. We then varied the efficacy to find bleed rates of factor VIII at the higher doses that would project the use of valoctocogene roxaparvovec and emicizumab to not be cost effective at threshold ratios of $50,000, $100,000, $150,000, and $200,000 per QALY.

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

1. 50/50 shared savings in which 50% of lifetime health care cost offsets from a new treatment are assigned to the health care system instead of being assigned entirely to the new treatment

2. 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

3. An optimistic scenario (starting at a factor level of 89 IU/dL and using the proportional decline seen from year 3 to 4 to project) and a conservative scenario (same starting point as the base case and using a linear projection of decline) to estimate projected trends in Factor level decline.

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

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

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

Model Validation

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

5.3 Results

Base Case Results

Table 5.10 describes the discounted lifetime total costs and outcomes from the two versions of the model. In the first version of the model, in both base-case analyses, valoctocogene roxaparvovec, at its placeholder price, is projected to have higher total costs, lower bleeds, and more QALYs associated with it. The base case in the second version of the model found that emicizumab was

associated with higher total costs, lower bleeds, and higher QALYs from the health sector perspective.

Table 5.10. Results for the Base-Case Versions of the Model Comparing Valoctocogene Roxaparvovec to Factor VIII in Adults and Emicizumab to Factor VIII for All Patients

Treatment	Drug Cost	Total Cost	Joint Bleeds	Treated Non-Target Joint Bleeds	Treated Target Joint Bleeds	Life Years	QALYs
Factor VIII (Model version1 – Health Sector Perspective)	$12,540,000	$13,243,000	89.73	28.97	31.53	26.53	19.015
Valoctocogene Roxaparvovec (Model version 1 – Health Sector Perspective)	$13,293,000	$13,694,000	43.13	15.06	17.56	26.53	19.092
Factor VIII (Model version 1 – Modified Societal Perspective)	$12,540,000	$13,313,000	89.73	28.97	31.53	26.53	19.015
Valoctocogene Roxaparvovec (Model version 1 – Modified Societal Perspective)	$13,293,000	$13,733,000	43.13	15.06	17.56	26.53	19.092
Factor VIII (Model version 2 – Health Sector Perspective)	$10,117,000	$10,650,000	76.78	23.07	23.37	29.14	23.858
Emicizumab (Model version 2 – Health Sector Perspective)	$13,316,000	$13,598,000	38.60	12.64	13.76	29.14	24.141

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

Table 5.11 describes the incremental cost and QALY results from the two versions of the model based on the base-case costs and QALYs shown above. In both base cases for version 1, valoctocogene roxaparvovec, at its placeholder price, had an incremental cost effectiveness ratio of over $5M compared to factor VIII. In the base case for version 2, emicizumab was found to have an incremental cost effectiveness ratio of over $10 M per QALY relative to factor VIII.

Table 5.11. Incremental Cost-Effectiveness Ratios for the Base Case

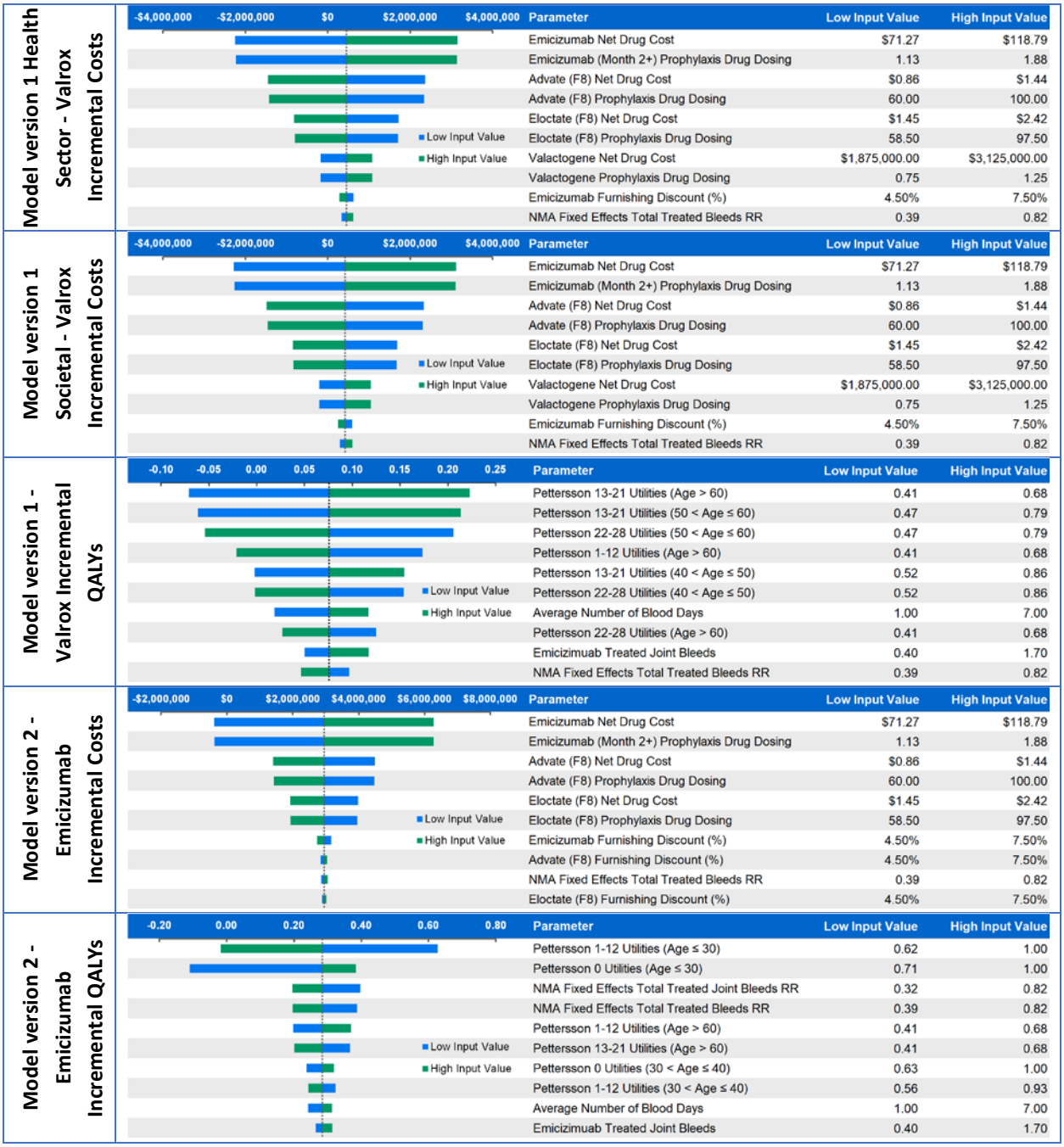
Treatment	Incremental Cost	Incremental QALYs	Incremental Cost-Effectiveness Ratio
Factor VIII (Model version 1 – Health Sector Perspective)	Reference	Reference	Reference
Valoctocogene Roxaparvovec (Model version 1 – Health Sector Perspective)	$452,000	0.076	$5,949,000/QALY gained
Factor VIII (Model version 1 – Modified Societal Perspective)	Reference	Reference	Reference
Valoctocogene Roxaparvovec (Model version 1 – Modified Societal Perspective)	$420,000	0.076	$5,531,000/QALY gained
Factor VIII (Model version 2 – Health Sector Perspective)	Reference	Reference	Reference
Emicizumab (Model version 2 – Health Sector Perspective)	$2,948,000	0.284	$10,393,000/QALY gained

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

Sensitivity Analysis Results

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e., standard errors from literature) or reasonable ranges (+/- 25%) to evaluate changes in incremental costs and in incremental QALYs for valoctocogene roxaparvovec, at its placeholder price, and emicizumab versus factor VIII. In version 1, the net drug cost of emicizumab and the dose were key drivers as patients beginning on valoctocogene roxaparvovec end up switching to emicizumab once projected factor levels become too low. The cost and dose of emicizumab had substantial influence in version 2 as well. In addition, the drug costs and prophylactic drug dosing have a substantial influence on the projected incremental costs in version 1 and version 2. The projected incremental QALYs in version 1 and 2 are relatively sensitive to the utilities associated with various PS in both models. The number of days per bleed has more of an influence on the incremental QALYs in version 1 than in version 2.

Figure 5.2. Tornado Diagram(s) for One-Way Sensitivity Analyses of Emicizumab/Valoctocogene Roxaparvovec versus Factor VIII



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

Table 5.12 summarizes the probabilistic sensitivity analyses showing the percent of simulations that project cost effectiveness for valoctocogene roxaparvovec and emicizumab relative to factor VIII at various standard thresholds for cost effectiveness. Despite the high incremental cost effectiveness ratios in the base-case results, valoctocogene roxaparvovec, at its placeholder price, was found to be cost effective in over 40% of the simulations at each of the selected threshold levels. , these

show that several of the inputs have both sufficient potential variance and influence on the first version of the model that in roughly 40% of the simulations there are potential sets of inputs that would give a different conclusion than that seen in the base case. Emicizumab, was found to be cost effective in only 14% of the simulations at each of the selected thresholds. For both drugs, the results in the scenario analyses using doses for factor VIII that are currently being used in the US also provide contrasting results as described below. The visual representation of the simulations on the cost-effectiveness plane can be found in the appendix under Figure E2. The 95% credible intervals and ranges can be found in the appendix Table E4.

Table 5.12. Probabilistic Sensitivity Analysis Results: Emicizumab/Valoctocogene Roxaparvovec versus Factor VIII

	Cost Effective at $50,000 per QALY	Cost Effective at $100,000 per QALY	Cost Effective at $150,000 per QALY	Cost Effective at $200,000 per QALY	Cost Effective at $250,000 per QALY
Valoctocogene Roxaparvovec (Model version 1 – Health Sector Perspective)	43.21%	43.28%	43.36%	43.35%	43.42%
Valoctocogene Roxaparvovec (Model version 1 – Modified Societal Perspective)	43.64%	43.65%	43.68%	43.83%	43.90%
Emicizumab (Model version 2)	14.00%	14.07%	14.26%	14.39%	14.5%

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

Scenario Analyses Results

Table 5.13 summarizes the results from the scenario analyses using the doses of factor VIII used in the base-case versions. In each of the scenarios applied to version 1, valoctocogene roxaparvovec, at its placeholder price, was found to have an incremental cost-effectiveness ratio well above standard thresholds, except for the scenario in which patients entered the model at age 40 with a Pettersson score of 20. In each of the scenarios applied to version 2, emicizumab was also found to have an incremental cost-effectiveness ratio well above standard thresholds. Below, however, we explore additional scenarios changing the dose of factor VIII to be more representative of the doses currently used in the US; this has a substantial impact on the results.

Table 5.13. Selected Scenario Analyses for Version 1 and 2 of the Model

Scenario	Model Version	Treatment	Incremental Cost	Incremental QALYs	Incremental Cost-Effectiveness Ratio
Higher Bleed Duration	1 Health Sector	Valoctocogene Roxaparvovec	$452,000	0.117	$3,860,000/QALY gained
	1 Societal	Valoctocogene Roxaparvovec	$420,000	0.117	$3,589,000/QALY gained
	2	Emicizumab	$2,948,000	0.314	$9,403,000/QALY gained
Higher Bleed Rate	1 Health Sector	Valoctocogene Roxaparvovec	$155,000	0.242	$642,000/QALY gained
	1 Societal	Valoctocogene Roxaparvovec	$92,000	0.242	$380,000/QALY gained
	2	Emicizumab	$2,756,000	0.351	$7,851,000/QALY gained
Societal	2	Emicizumab	$2,925,000	0.284	$10,313,000/QALY gained
Older Age (40) and Pettersson Score (20) Start	1 Health Sector	Valoctocogene Roxaparvovec	-$479,000	0.065	Dominant
	1 Societal	Valoctocogene Roxaparvovec	-$505,000	0.065	Dominant
Pettersson Score Return to 13	1 Health Sector	Valoctocogene Roxaparvovec	$452,000	0.076	$5,949,000/QALY gained
	1 Societal	Valoctocogene Roxaparvovec	$420,000	0.076	$5,531,000/QALY gained
	2	Emicizumab	$2,948,000	0.284	$10,393,000/QALY gained

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

Table 5.14 summarizes the SST framework scenario analyses applied to valoctocogene roxaparvovec as compared with factor VIII. Splitting and capping the level of cost savings for valoctocogene roxaparvovec has a substantial impact moving the incremental cost-effectiveness ratio for valoctocogene roxaparvovec, at its placeholder price, to more than $90M per QALY. In the optimistic scenario for valoctocogene roxaparvovec, it becomes a dominant treatment. In all the other SST scenarios, the incremental ratios are all well above commonly used thresholds. Again, however, see the scenario analyses below using representative doses of factor VIII.

Table 5.14. Incremental Costs and QALYs in the SST Scenario Analyses

Scenario	Model Version	Treatment	Incremental Cost	Incremental QALYs	Incremental Cost-Effectiveness Ratio
50/50 Cost Sharing	Health Sector	Valoctocogene Roxaparvovec	$7,129,000	0.076	$93,914,000/QALY gained
	Societal	Valoctocogene Roxaparvovec	$7,133,000	0.076	$93,959,000/QALY gained
Cap Offset costs at $150,000/Year*	Health Sector	Valoctocogene Roxaparvovec	$9,130,000	0.076	$120,268,000/QALY gained
	Societal	Valoctocogene Roxaparvovec	$9,169,000	0.076	$120,777,000/QALY gained
Conservative Valoctocogene Projection	Health Sector	Valoctocogene Roxaparvovec	$2,212,000	0.084	$26,269,000/QALY gained
	Societal	Valoctocogene Roxaparvovec	$2,177,000	0.084	$25,852,000/QALY gained
Optimistic Valoctocogene Projection	Health Sector	Valoctocogene Roxaparvovec	-$733,000	0.081	Dominant
	Societal	Valoctocogene Roxaparvovec	-$766,000	0.081	Dominant
Payment Scenario	Health Sector	Valoctocogene Roxaparvovec	$445,000	0.078	$5,741,000/QALY gained
	Societal	Valoctocogene Roxaparvovec	$413,000	0.078	$5,323,000/QALY gained

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

Threshold Analyses Results

Base Case Model

Note that these results are preliminary and for reasons discussed in Chapter 7 should not be assumed to reflect the health-benefit price benchmarks that will be provided for emicizumab in the next version of this report; as discussed previously, health-benefit price benchmarks will not be provided for valoctocogene roxaparvovec. Table 5.15 shows threshold prices that would result in cost-effectiveness ratios of $50,000, $100,000, $150,000 and $200,000 per QALY for the base-case versions of the model. As mentioned above, because the model assumed no differential mortality effect of prophylaxis options for hemophilia A in patients without inhibitors, threshold analysis results for equal value life years gained (evLYG) would be identical to those for costs per QALY projected by the model.

Table 5.15. Threshold Analysis Results for the Base Case

Scenario	WAC per unit	Net Price per unit	Unit Price to Achieve $50,000 per QALY	Unit Price to Achieve $100,000 per QALY	Unit Price to Achieve $150,000 per QALY	Unit Price to Achieve $200,000 per QALY
Valoctocogene Roxaparvovec (Model Version 1 – Health Sector Perspective)	$2,500,000	$2,500,000	$2,052,000	$2,056,000	$2,069,000	$2,064,000
Valoctocogene Roxaparvovec (Model Version 1 – Modified Societal Perspective)	$2,500,000	$2,500,000	$2,084,000	$2,088,000	$2,091,000	$2,095,000
Emicizumab (Model Version 2 – Health Sector Perspective)	$100.19/mg	$83.68/mg	$74.09/mg	$74.19/mg	$74.29/mg	$74.39/mg

WAC and net prices for valoctocogene roxaparvovec are placeholder prices

SST Scenarios

We found that the 50/50 split and the capped cost saving SST scenarios were not appropriate for producing threshold prices for valoctocogene roxaparvovec due to the decline in efficacy across time for this treatment and the subsequent shift to other prophylaxis treatment. Therefore, we will consider other scenario analyses for inclusion in the Evidence Report. In the other SST scenarios, only in the optimistic projection of valoctocogene roxaparvovec, using its placeholder price, was it found to be a dominant treatment.

Impact of Using Doses of Factor VIII More Representative of Current Use in the US

An important variable in version 2 was the dose of factor VIII, and hence we examined a version of the model using representative doses of factor VIII as opposed to doses that reflect the use of factor VIII in the trial from which the efficacy data came from. Specifically, we used a dose of 118.2 IU/kg for Advate and 111.2 IU/kg for Eloctate. At those doses, the prophylactic costs of factor VIII were projected to be $18,269,000 and $14,821,000 in versions 1 and 2 of the model and the health care perspective total costs were $18,971,000 and $15,297,000 respectively in versions 1 and 2 (see Table 5.16 below). With those costs and the same efficacy of factor VIII as seen in the trial, valoctocogene roxaparvovec, at its placeholder price, was projected to save over $5M and emicizumab was projected to save $1.7 million dollars with each having higher QALYs in versions 1 and 2 of the model. Furthermore, at those dose levels, even if factor VIII resulted in zero bleeds per year over a lifetime, valoctocogene roxaparvovec, at its placeholder price, and emicizumab would

still be considered cost effective at a willingness to pay threshold of $150,000 per QALY. For example, with the zero-bleed assumption, factor VIII would be projected to produce over 2 additional QALYs relative to emicizumab but would cost $1.2 million additional dollars.

Table 5.16. Model Projections using Representative Doses for Factor VIII

Treatment	Total Cost	QALYs
Factor VIII (Model version1 – Health Sector Perspective)	$18,971,000	19.015
Valoctocogene Roxaparvovec (Model version 1 – Health Sector Perspective)	$13,694,000	19.092
Factor VIII (Model version 1 – Modified Societal Perspective)	$19,041,000	19.015
Valoctocogene Roxaparvovec (Model version 1 – Modified Societal Perspective)	$13,733,000	19.092
Factor VIII (Model version 2 – Health Sector Perspective)	$15,297,000	23.858
Emicizumab (Model version 2 – Health Sector Perspective)	$13,598,000	24.141

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

Model Validation

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

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

Prior Economic Models

A 2017 ICER report reviewed hemophilia A individuals with inhibitors and included discussions regarding prior economic analyses. Details on those economic analyses can be seen in that report.

Since the 2017 ICER report, there have been several related models published in the literature. Coppola et al. in 2017 focused on prophylaxis versus on demand treatment with factor VIII, based on historical data for patients aged 12 and over in Italy. This model used annual cycles and tracked PS from 0-78 across time based on an increase in PS for every 6.52 bleeds for patients younger than 25 and by one for every 36.52 bleeds after the age of 25. Surgery is separately included in the

model based on annual proportions of patients requiring surgery and is not attached nor does it impact PS in their model. The dose used for factor VIII prophylaxis was 75 IU/kg per week, close to the dose seen in the trial we used as our base case and their bleed rates at that dose were fairly similar to those in our model.

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

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

In addition to using a relatively high dose of Eloctate, and using only Eloctate, in the model they used a relatively high cost of $1.63 per IU. They also used a cost for valoctocogene roxaparvovec of $2,000,000, and a cost of surgery of $40,560. The utility scores in the Cook model associated with bleeds and the duration for bleeds were similar to our model; however, their model incorporated a separate disutility of factor VIII infusions of 0.0004 per infusion. In addition, surgery-related utility as well as the utilities across PS were somewhat different, and declined across levels of PS all the way to 78. Overall, their model found more cost savings and slightly higher QALY gains associated with valoctocogene roxaparvovec than our model, but was consistent in terms of finding the

treatment dominant. Most of the difference in the incremental utility results are because of the disutility used for infusions, and most of the cost differences are related to the higher dose of Eloctate and higher cost per IU.

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

Uncertainty and Controversies

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

Most importantly, the dose of factor VIII is a key driver in the model. In fact, when using doses for factor VIII derived from the underlying trial that was used to estimate efficacy in the model, factor VIII appears very cost effective compared with valoctocogene roxaparvovec, at its placeholder price,

and emicizumab. However, when incorporating representative doses of factor VIII currently seen in the US, the model projects that valoctocogene roxaparvovec, at its placeholder price, and emicizumab are both dominant treatments and that even if factor VIII were curative at those higher doses it would still not be cost effective.

Limitations

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

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

We are using a placeholder price for valoctocogene roxaparvovec.

5.4 Summary and Comment

In this analysis of valoctocogene roxaparvovec, now deemed preliminary due to initial rejection by the FDA of its licensing application and using a placeholder price of $2.5 million, the therapy was found to not be cost effective for adult patients with hemophilia A without inhibitors at standard cost-effectiveness thresholds when using doses of factor VIII consistent with the underlying trial used in the NMA. This finding, however, varied in the sensitivity analyses and importantly was completely reversed when the model incorporated doses of factor VIII that are more representative of current use in the US. Given that valoctocogene roxaparvovec meets ICER's criteria to be considered a high-impact single and short-term therapy, we performed two additional scenario analyses. In one of these scenarios, 50% of the modeled cost savings from treatment are "retained" by the health system instead of being ascribed to the therapy; in the other, cost savings from treatment beyond $150,000 are retained by the health system. In both of these alternative scenarios, valoctocogene roxaparvovec, at its placeholder price, was found to have extremely high incremental cost-effectiveness ratios, reflecting the very high current costs of treating people with hemophilia A with factor VIII. The purpose of producing these alternative scenarios is to provide empirical findings that may stimulate public dialogue on whether and how extremely large cost offsets should be incorporated in judgments of reasonable pricing for novel therapies that are delivered as single or short-term interventions.

The cost effectiveness of emicizumab in patients with hemophilia A without inhibitors was also highly dependent on what it is being compared to. The base-case analysis for emicizumab

compared it to the average dose of factor VIII for prophylaxis used in the trial from which we derived comparative efficacy data (80 IU/kg). At this dose, emicizumab provides additional net benefit but does not meet standard cost-effectiveness thresholds. However, at the higher doses of factor VIII currently being used in the US, and with an increasing proportion of patients receiving more expensive extended half-life preparations, our model suggests that emicizumab is highly cost saving. We are uncertain of the added efficacy of these higher doses, but even if these doses completely eliminated all bleeding events (and thus had greater efficacy than emicizumab), emicizumab would remain cost effective. As such, at the doses of factor VIII currently being used for prophylaxis in the US, payers would be expected to see cost savings if patients switched to emicizumab.

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

6. Potential Other Benefits and Contextual Considerations

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

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

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

Table 6.1. Categories of Potential Other Benefit and Contextual Considerations

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

6.1 Potential Other Benefits and Contextual Considerations

Both emicizumab and valoctocogene roxaparvovec are likely to somewhat improve productivity of patients with hemophilia A.

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

Emicizumab

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

Administration of emicizumab is substantially easier than administration of factor VIII as it is given by subcutaneous injection rather than intravenous infusion making it easier and quicker to administer. It is also administered much less frequently than factor VIII. It is likely that this will both improve adherence and result in some patients choosing prophylaxis who were previously only willing to use on-demand therapy. Additionally, in infants and young children administration of factor VIII may require an implanted port that can result in complications such as infections and clotting. Adherence to emicizumab is likely to more closely approximate that seen in clinical trials than adherence to factor VIII prophylaxis.

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

Valoctocogene Roxaparvovec

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

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

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

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

QALY Shortfalls

One important contextual consideration to consider is the argument that society should give preference to treatments for patients with more severe conditions[76], and that giving priority to treatments according to "lifetime burden of illness" or "need" best represents the ethical instincts of a society or other decision-makers.[77,78] To inform this contextual consideration, ICER provides empirical results for the absolute QALY shortfall and proportional QALY shortfall. The absolute QALY shortfall is defined as the total absolute amount of future health patients with a condition are expected to lose without the treatment that is being assessed.[79] The ethical consequences of using absolute QALY shortfall to prioritize treatments is that conditions that cause early death or that have very serious lifelong effects on quality of life receive the greatest prioritization. Thus, certain kinds of treatments, such as treatments for rapidly fatal conditions of children, or for lifelong disabling conditions, score highest on the scale of absolute QALY shortfall.

The proportional QALY shortfall is measured by calculating the proportion of the total QALYs of remaining life expectancy that would be lost due to untreated illness.[80,81] The proportional QALY shortfall reflects the ethical instinct to prioritize treatments for patients whose illness would rob them of a large percentage of their expected remaining lifetime. As with absolute QALY shortfall, rapidly fatal conditions of childhood have high proportional QALY shortfalls, but the highest numbers can also often arise from severe conditions among the elderly who may have only a few years left of average life expectancy but would lose much of that to the illness without treatment.

For this population of hemophilia A patients without inhibitors, the absolute shortfall was estimated to be 13.3 QALYs, with a proportional shortfall of 0.26, representing a loss of 26% of total quality-adjusted life expectancy (QALE) without the condition. (Note that this estimate is impacted by our assumption that there is no mortality effect from prophylaxis for hemophilia A in patients without inhibitors.) To provide some anchoring of these results, we also present a league table of absolute and proportional QALY shortfalls for a variety of conditions from prior ICER reports (Table 6.2), using a burden of disease calculator developed by Dutch investigators (https://imta.shinyapps.io/iDBC/) that allows for calculation of absolute and proportional QALY shortfalls under different assumptions.[78]

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

	From ICER reports			From iDBC tool[82]	
Condition	Age	% Male	Total Undiscounted QALYs with Standard of Care	Absolute Shortfall	Proportional Shortfall
Hemophilia A	18	100	38.6	13.3	0.26
Secondary Progressive Multiple Sclerosis	48	39	3.0	24.5	0.89
Treatment-resistant Major Depression	46	33	20.5	8.7	0.30
Cystic Fibrosis	2	52	25.8	42.3	0.62

QALY: quality-adjusted life year

7. Health Benefit Price Benchmarks

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.

Health benefit price benchmarks for emicizumab will be included in the revised Evidence Report that will be released on or about October 22, 2020. Given the FDA decision to issue a CRL for valoctocogene roxaparvovec, ICER will not be including health benefit price benchmarks for valoctocogene roxaparvovec in the Evidence Report.

8. Potential Budget Impact

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

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

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APPENDICES

Appendix A. Search Strategic Results

Table A.1. PRISMA 2009 Checklist

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

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

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

Table A.2. Search Strategies for Valoctocogene roxaparvovec, emicizumab and FVIII Inhibitors for Hemophilia A

Table A.2.1: Search Strategy for Interventions: Medline 1996 to Present with Daily Update, and Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations

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

Table A.2.2. Search strategy for Interventions: EMBASE SEARCH

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

Table A.2.3: Search Strategy for Comparators: Medline 1996 to Present with Daily Update, and Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations

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

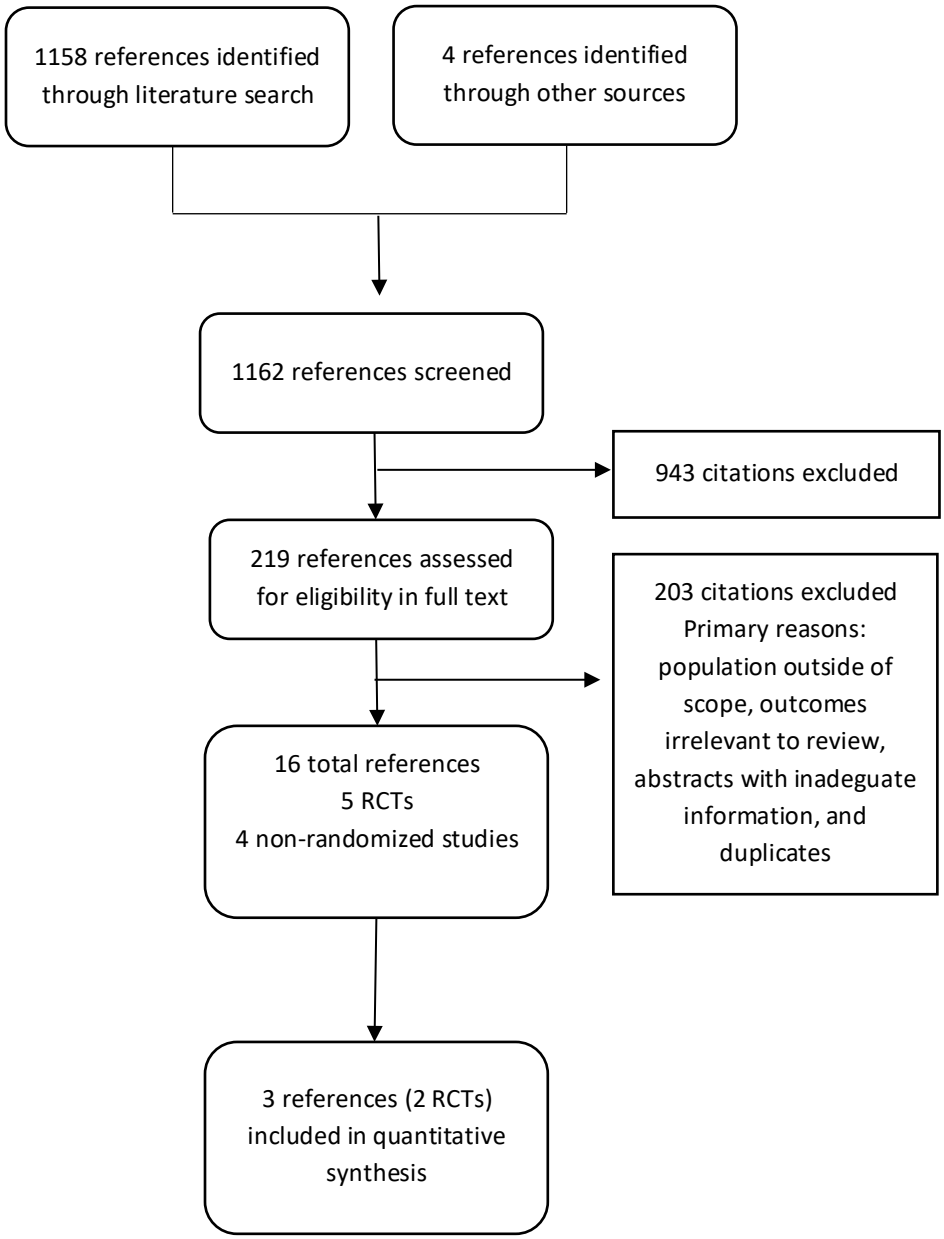
10	(afstyla or rviii-sc or rfviii sc).ti,ab
11	(eloctate or biib031 or rfviiifc or elocta* or elocta or efmoroctocog alfa).ti,ab
12	(humate-p or humate p or haemate-p or haemate p).ti,ab
13	(jivi or bay94-9027 or bay94 9027 or BAY 94 -9027 or BAY 94 9027).ti,ab
14	(kogenate fs or kogenate bayer or bay14-2222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

Table A.2.4. Search strategy for Comparators: EMBASE SEARCH

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

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

Figure A.1. PRISMA flow Chart Showing Results of Literature Search for Valoctocogene roxaparvovec, emicizumab and FVIII Inhibitors for Hemophilia A



Appendix B. Previous Systematic Reviews and Technology Assessments

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

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

Appendix C. Ongoing Studies

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

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

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

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

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

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

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

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

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

Appendix D. Comparative Clinical Effectiveness Supplemental Information

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

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

We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories "good," "fair," or "poor" (see Appendix Table F2) [83] Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

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

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

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

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

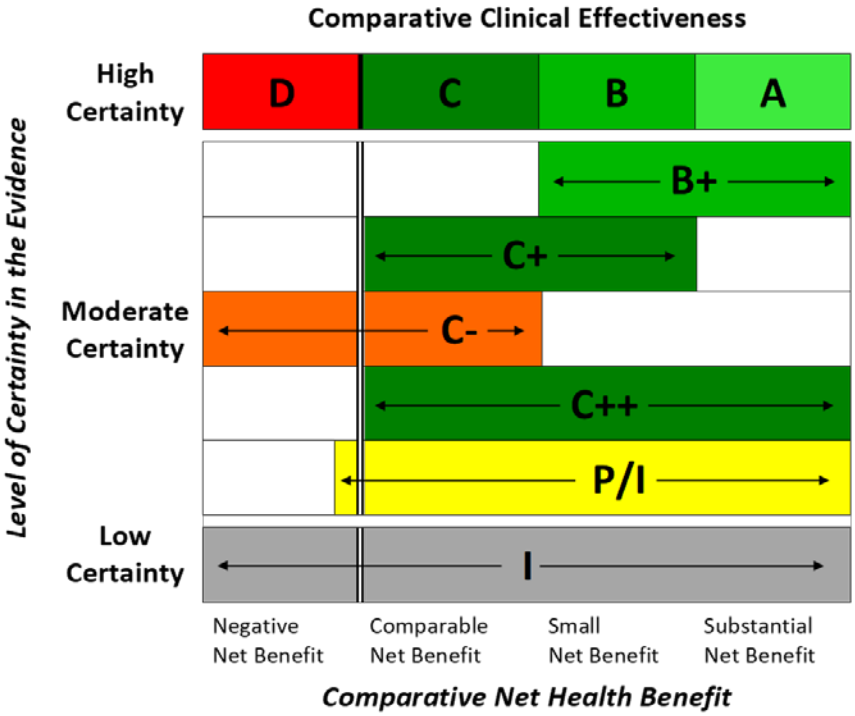
ICER Evidence Rating

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

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

7. The level of certainty in the best point estimate of net health benefit.[30,31]

Figure D.1. ICER Evidence Rating Matrix



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

Abstraction Tables

Table D1. Valoctocogene Roxaparvovec and Emicizumab

Author & Year of Publication (Trial) Quality Rating	Study Design and Duration of Follow-up	Inclusion and Exclusion Criteria	Interventions (n) & Dosing Schedule	Patient Characteristics	Outcomes	Harms
Emicizumab						
Mahlangu NEJM 2018[33] (HAVEN 3) *Good quality*	Phase 3, open-label, randomized trial Follow up: At least 24 weeks 39 sites in 13 countries (United States, Australia, Costa Rica, France, Germany, Ireland, Italy, Japan, Japan, Korea, Poland, South Africa, Spain, Taiwan, United Kingdom)	**Inclusion** -12 years of age or older - severe hemophilia A without inhibitors to factor VIII -Previously receiving episodic or prophylactic treatment with FVIII therapy **Exclusion** -Inherited or acquired bleeding disorder other than hemophilia A -Treatment within the last 12 months for, or current signs of, thromboembolic disease	**Patients on prior episodic FVIII treatment were randomized to:** 1) Emicizumab SC 1.5mg/kg weekly (n =36) 2) Emicizumab SC 3mg/kg every other weekly (n =35) 3) No prophylaxis (n=18) **All patients previously on adequate prophylactic FVIII were assigned to:** 4) Emicizumab SC 1.5mg/kg weekly (n =63) All patients were given loading doses of 3 mg/kg per week for 4 weeks Patients could receive FVIII (investigation-	**Median Age (range)** (1) 37 (19-77) (2) 41 (20-65) (3) 40 (16-57) (4) 36 (13-68) **Male, %** 100% male in all groups **Participants without FVIII inhibitors, %** 100% in all groups **Severe Hemophilia, %** 100% in all group (based on inclusion criteria) **Presence of target Joint, n (%)** (1) 34 (94) (2) 27 (77) (3) 15 (83)	**Randomized comparison in patients on prior episodic treatment:** **Model based ABR (95% CI); p-value vs. group 3 at week 24** *Treated bleeds* (1) 1.5 (0.9-2.5) ; P,0.001 (2) 1.3 (0.8-2.3) ; P<0.001 (3) 38.2 (22.9-63.8) *All (treated & untreated)* (1) 2.5 (1.6-3.9) ; P<0.001 (2) 2.6 (1.6-4.3) ; P<0.001 (3) 47.6 (28.5-79.6) *Treated joint bleeds* (1) 1.1 (0.6-1.9) ; P<0.001 (2) 0.9 (0.4-1.7) ; -P<0.001 (3) 26.5 (14.7-47.8) *Treated target joint bleeds* (1) 0.6 (0.3-1.4) ; P<0.001 (2) 0.7 (0.3-1.6) ; P<0.001 (3) 13.0 (5.2-32.3) **Quality of life, difference in Haem-A-QOL vs. control (95% CI)** (1) 12.5 (-2.0-27.0) (2) 16.0 (1.2-30.8) (3) control	**All patients** **Mortality, n(%)** (1) 0 (0%) (2) 0 (0%) (3) 0 (0%) (4) 0 (0%) **Serious AEs, N** (1) 1 (2) 3 (3) 0 (4) 0 **Thrombosis, n(%)** (1) NR (2) NR (3) NR (4) NR **Injection-Site reaction, n(%)** (1) 9(25%) (2) 7(20%) (3) 2(12%) (4) 20(32%)

Author & Year of Publication (Trial) Quality Rating	Study Design and Duration of Follow-up	Inclusion and Exclusion Criteria	Interventions (n) & Dosing Schedule	Patient Characteristics	Outcomes	Harms
			determined doses) for breakthrough bleeding	(4) 26 (41) **<9 bleeds in 24 wks prior to trial, n (%)** (1) 9 (25) (2) 5 (14) (3) 4 (22) (3) 53 (84)		
Mahlangu NEJM 2018[33] (HAVEN 3 – intra-individual comparison) *Good quality* (Additional References: Oldenburg 2019[34])	Phase 3, open-label, randomized trial (*See Mahlangu NEJM 2018 above)* Design was open label for the intra-individual comparison Majority of patients that participated in open label emicizumab participated in prior prospective non-interventional study (NIS) for at least at least 24 weeks	*See Mahlangu NEJM 2018 above*	**Patients previously on adequate prophylactic FVIII who had participated in a NIS** 1) Factor VIII prophylaxis during NIS (n=48) 2) Emicizumab SC 1.5mg/kg weekly during HAVEN 3 (n =48)	**Patients specifically in NIS not reported** *(See Mahlangu NEJM 2018 above for all patients)*	**<u>Intra-individual comparison in patients on prior adequate prophylactic FVIII</u>** **<u>Randomized comparison in patients on prior episodic treatment:</u>** **Model based ABR (95% CI); p-value vs. group 3** *Treated bleeds* (1) 1.6 (1.1-2.4) ; P<0.001 (2) 4.8 (3.2-7.1) *All (treated & untreated)* (1) 3.3 (2.2-4.8); p<0.0002 (2) 8.9 (5.7-13.9) *Treated joint bleeds* (1) 1.2 (0.7-2.0) (2) NA *Treated target joint bleeds* (1) 0.6 (0.3-1.5)	*See Mahlangu NEJM 2018 above for all patients*

Author & Year of Publication (Trial) Quality Rating	Study Design and Duration of Follow-up	Inclusion and Exclusion Criteria	Interventions (n) & Dosing Schedule	Patient Characteristics	Outcomes	Harms
					(2) NA **Quality of life, difference in Haem-A-QOL vs. control (95% CI)** (1) NR (2) NR	
Pipe Lancet 2019[35] (HAVEN 4) (Additional references: Skinner 2019[38])	Phase 3, open-label, multicenter, 2-stage trial (run-in phase* to assess pharmacokinetics & expansion phase to assess efficacy) Follow up: At least 24 weeks 17 sites in 6 countries (Australia, Belgium, Japan, Poland, Spain, and the USA) *Run-in phase not abstracted	**Inclusion** -12 years of age or older -Severe hemophilia A or hemophilia with inhibitors undergoing treatments with FVIII concentrates or bypassing agents -Patients on episodic treatment were required to have ≥5 bleeds in the 24 weeks before study entry **Exclusion** -Patients who are at high risk for thrombotic microangiopathy -previous (within 12 months) or current thrombotic disease	**Patients on prior episodic FVIII treatment were randomized to:** 1) Emicizumab SC 6mg/kg weekly (n =41) Patients were given loading doses of 3 mg/kg per week for 4 weeks Patients could receive FVIII (investigation-determined doses) for breakthrough bleeding	**Median Age (range)** (1) 39 (14-68) **Male, n (%)** (1) 41 (100) **Participants without FVIII inhibitors, n (%)** (1) 36 (88) **Severe Hemophilia, %** (1) 40 (98) **Presence of target Joint, n (%)** (1) 25 (61) **Median number of bleeds in the 24 wks prior to trial (range)** (1) 5 (0-90)	<u>**Patients on prior episodic FVIII treatment:**</u> **Model based ABR (95% CI)** *Treated bleeds* (1) 2.4 (1.4-4.3) *All (treated & untreated)* (1) 4.5 (3.1-6.6) *Treated joint bleeds* (1) 1.7 (0.8-3.7) *Treated target joint bleeds* (1) 1.0 (0.3-3.3) **Pooled Quality of life Haem-A-QoL changes from BL in participants ≥18, mean (SD)** <u>Week 25</u> -15.1 (21.9) <u>Week 49</u> -17.4 (20.6) <u>Week 61</u> -18.4 (23.2) <u>Week 73</u>	**Serious AE** (1) 1(2%) **AE leading to withdrawal from treatment** (1) 0(0%) **AE leading to dose modification or interruption** (1) 0 (0%) **Treatment related AE** (1) 12(29%) **Treatment related local injection-site reaction** (1) 9(22%) **Grade ≥3** (1) 1(2%) **Grade 2** (1) 14(34%)

Author & Year of Publication (Trial) Quality Rating	Study Design and Duration of Follow-up	Inclusion and Exclusion Criteria	Interventions (n) & Dosing Schedule	Patient Characteristics	Outcomes	Harms
					NE	**Grade 1** (1) 15(37%) **Nasopharyngitis** (1) 11(27%)
Callaghan 2019[37] (abstract)	Pooled data on long-term efficacy and safety of emicizumab in phase III studies Follow-up: 98 weeks	**Inclusion** -Pediatric and adolescent/adult PwHA -With or without inhibitors -All patients assigned to emicizumab **Exclusion** NR	1)Haven 1 (n=113) 2) Haven 2 (n=88) 3) Haven 3 (n=151) 4) Haven 4 (n=48) *only reporting data from Haven 3 and 4	*See Mahlangu NEMJ 2018 and Pipe Lancet 2019 above*	**Pooled Mean Annualized Bleed Rate in Patients Taking Emicizumab in HAVEN 3 and 4 (95% CI)** <u>1-24 weeks</u> 3) 1.8 (0.2-7.0) 4) 2.1 (0.3-7.4) <u>25-48 weeks</u> 3) 0.9-0.0-5.5) 4) 1.5 (0.1-6.4) <u>49-72 weeks</u> 3) 0.9 (0.0-5.5) 4) NE <u>73-96 weeks</u> 3) 0.2 (0.0-4.1) 4) NE	*See Mahlangu NEMJ 2018 and Pipe Lancet 2019 above*
Shima Hemophilia 2019[36] (HOHOEMI)	Multicenter, open-label, non-randomized, efficacy, safety, and pharmacokinetics Follow-up: at least 24 weeks	**Inclusion** -<12 years old, weighing over 3kg -Severe congenital hemophilia A without FVIII inhibitors -Tested negative for inhibitors within 8	1)maintenance dose of 3mg/kg emicizumab Q2W (n=6) 2)maintenance dose of 6mg/kg emicizumab Q4W (n=7)	**Age (y), median (range)** (1) 6.6 (1.5-10.7) (2) 4.1 (0.3-8.1) **Weight (kg), median (range)** (1) 19.5 (10.9-35.6) (2) 15.7 (6.6-25.6)	**Model based ABR (95% CI)** *Treated bleeds* (1) 1.3 (0.6-2.9) (2)0.7 (0.2-2.6) *All (treated & untreated)* (1) 14.1 (7.6-26.2) (2) 21.8 (9.2-51.8) *Treated joint bleeds*	No thromboembolic events, TMA, or systematic hypersensitivity reactions were observed. Only one event of injection site reaction was

Author & Year of Publication (Trial) Quality Rating	Study Design and Duration of Follow-up	Inclusion and Exclusion Criteria	Interventions (n) & Dosing Schedule	Patient Characteristics	Outcomes	Harms
	4 centers in Japan	weeks prior to enrollment -Documentation of bleeding episodes and treatment with coagulation factors was required in 12 weeks prior to enrollment for patients <2 years old and 24 weeks prior for patients ≥2 years old **Exclusion** -Complication of a bleeding disorder other than hemophilia a -thromboembolic diseases within the past 12 months -High risk of thrombotic microangiopathy (TMA) -or familial history of TMA	Each cohort received a loading dose of 3 mg/kg QW for the first 4 weeks Patients who had received FVIII prophylaxis prior to enrollment were permitted to continue FVIII prophylaxis until receiving the second loading dose of emicizumab. FVIII products were administered for breakthrough bleeding, as necessary.	**Patients treated with FVIII prophylaxis prior to enrollment, n(%)** (1) 6(100%) (2) 6(85.7) **Previously untreated patients (PUPs), n(%)** (1) 0(0%) (2) 1(14.3) **Patients with target joints, n(%)** (1) 1 (16.7%) (2) 0 (0%)	(1) 0.9 (0.3-2.3) (2) NE *Treated target joint bleeds* (1) NE (2) NE	considered to be related to treatment in the Q2W cohort and was resolved without any treatment **Total patients with ≥AE, n(%)** (1) 6 (100%) (2) 7 (100%) **Nasopharyngitis n(%)** (1) 2 (33.3%) (2) 3(42.9) **Contusion, n(%)** (1) 4 (66.7) (2) 6 (85.7)
Valoctocogene Roxaparvovec						
Rangarajan 2017[18] **Pasi 2020**[17] Phase I/II	Phase I/II, multicenter, dose escalation, safety, and efficacy study	**Inclusion** -Adults with hemophilia a	1) Cohort 1 Low dose 6x10^12 vg/kg (n=1)**	**Median age (range)** (1) 25 (NA) (2) 43 (NA)	**Cohort 3 Results** **FVIII Activity Level** CS / OS	**Any AE** (1) 100% (2) 100% (3) 100%

<table>
<tr><th>Author & Year of Publication (Trial) Quality Rating</th><th>Study Design and Duration of Follow-up</th><th>Inclusion and Exclusion Criteria</th><th>Interventions (n) & Dosing Schedule</th><th>Patient Characteristics</th><th>Outcomes</th><th>Harms</th></tr>
<tr>
<td>Additional Publications: BioMarin PowerPoint[39], BioMarin R&D[40], BioMarin WFH Conference presentation[47,48]</td>
<td><u>Follow-Up:</u> up to 3 years
5 sites in the united kingdom</td>
<td>-No history of FVIII inhibitor development
-At least 50 days of previous exposure to FVIII concentrate
Patients on on-demand therapy
-at least 12 bleeding events (defined as a bleed event requiring FVIII replacement treatment) in previous 12 months were required

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

**Data for cohort 1 and 2 not reported

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

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

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

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

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

<table>
<tr><th>Author & Year of Publication (Trial) Quality Rating</th><th>Study Design and Duration of Follow-up</th><th>Inclusion and Exclusion Criteria</th><th>Interventions (n) & Dosing Schedule</th><th>Patient Characteristics</th><th>Outcomes</th><th>Harms</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>
<table>
<tr><td>Week 104</td><td>5</td><td>86.2</td></tr>
<tr><td>Week 156</td><td>6</td><td>87.0</td></tr>
<tr><td>Week 208</td><td>5</td><td>88.0</td></tr>
</table>
</td><td></td></tr>
<tr><td>Rangarajan 2017[18]
Pasi 2020[17]

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Additional Publications: BioMarin PowerPoint[39], BioMarin R&D[40], BioMarin WFH conference presentation[47,48]</td><td>See Rangarajan 2017 above</td><td>See Rangarajan 2017 above</td><td>1) Cohort 1 Low dose 6x10^12 vg/kg (n=1)**
2) Cohort 2 Intermediate dose 2x10^13 vg/kg (n=1)**
3) Cohort 3 high dose 6x10^13 vg/kg (n=7)
4) Cohort 4 4x10^13 vg/kg (n=5)*

*Only 2 years of data is available for patients in cohort 4</td><td>See Rangarajan 2017 above</td><td><u>Cohort 4 Results</u>
FVIII Activity Level
<table>
<tr><th></th><th>CS Mean (median)</th><th>OS Mean (Median)</th></tr>
<tr><td colspan="3">Cohort 4</td></tr>
<tr><td>Y1</td><td>21.0 (23)</td><td>31 (32)</td></tr>
<tr><td>Y2</td><td>15 (13)</td><td>23 (24)</td></tr>
<tr><td>Y3</td><td>9.9 (7.9)</td><td>14.9(12.3)</td></tr>
<tr><td>Y4</td><td>N/A</td><td>N/A</td></tr>
</table>
Annualized FVIII Usage
<table>
<tr><th></th><th>Mean (IU/dL)</th><th>% Reduced</th></tr>
<tr><td colspan="3">Cohort 4</td></tr>
<tr><td>BL</td><td>146.5</td><td rowspan="4">96%</td></tr>
<tr><td>Y1</td><td>2</td></tr>
<tr><td>Y2</td><td>6.8</td></tr>
<tr><td>Y3</td><td>8.4</td></tr>
<tr><td>Y4</td><td>N/A</td><td>N/A</td></tr>
</table>
Annualized Bleeding Rate
<table>
<tr><th></th><th>Mean</th><th>Median</th><th>N w/ Bleed</th></tr>
<tr><td colspan="4">Cohort 4</td></tr>
<tr><td>BL</td><td>12.2</td><td>8</td><td>17</td></tr>
<tr><td>Y1</td><td>0.9</td><td>0</td><td>83</td></tr>
<tr><td>Y2</td><td>1.2</td><td>0</td><td>67</td></tr>
<tr><td>Y3</td><td>0.5</td><td>0</td><td>67</td></tr>
<tr><td>Y4</td><td>N/A</td><td>N/A</td><td>N/A</td></tr>
</table>
</td><td>See Rangarajan 2017 above</td></tr>
</table>

Author & Year of Publication (Trial) Quality Rating	Study Design and Duration of Follow-up	Inclusion and Exclusion Criteria	Interventions (n) & Dosing Schedule	Patient Characteristics	Outcomes	Harms
					% 93% **Mean Total Score in HrQoL** **N** / **Cohort 4** **Week 0** 6 80.9 **Week 52** 4 82.4 **Week 104** 6 77.7 **Week 156** 6 83.0 **Week 208** N/A N/A	
BioMarin Press Release[41] **BioMarin Powerpoint**[39] **Phase III GENEr8-1**	Phase III, open-label single arm study, Follow-up 26 weeks	**Inclusion** -Males >18 years old =hemophilia A diagnosis and residual FVIII levels ≤ 1 IU/dL -Must be on prophylactic FVIII therapy for at least 12 months prior to study entry -No history of FVIIII inhibitor -HIV positive patients may be enrolled **Exclusion** -Detectable pre-existing antibodies to the AAV5 capsid -Any evidence of active infection or immunosuppressive disorder, except HIV	1) valoctocogene roxaparvovec 6E13 vg/kg (n=20)	*Not Yet Reported*	**Annualized Bleeding Rate (n=16)** Pre-Infusion Median: 0.9 Mean: 9.9 Post-Infusion Median: 0 Mean: 1.5 % Reduction: 85% **Annualized FVIII Usage (n=16)** Pre-infusion Median: 132.7 Mean: 146.1 Post-Infusion Median: 1.2 Mean: 6.6 % Reduction: 95% **FVIII Activity at 23-26 weeks (N= 16)** Max: 84.0 Mean: 36.3 Median: 33.1 Min: <1	No patients withdrew from the study **Serious Adverse Events** (1) 3(13.6) **ALT Elevation** (1) 17(77.3) **Nausea** (1) 11 (50) **Headache** (1) 10 (45.5) **Fatigue** (1) 9 (40.9) **AST** (1) 8 (36.4)

Author & Year of Publication (Trial) Quality Rating	Study Design and Duration of Follow-up	Inclusion and Exclusion Criteria	Interventions (n) & Dosing Schedule	Patient Characteristics	Outcomes	Harms
		-Active malignancy, except non-melanoma skin cancer				
BioMarin Press Release[41] **Phase III GENEr8-2**	Phase III, open-label single arm study, Follow-up: unclear	*See above GENEr8-1 study*	1) valoctocogene roxaparvovec 4E13 vg/kg (n=20) *dose seems to have been discontinued	*Not yet Reported*	*Not yet Reported*	*Not yet Reported*

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

Table D2. FVIII Studies

Author & Year of Publication (Trial) Quality Rating	Study Design and Duration of Follow-up	Inclusion and Exclusion Criteria	Interventions (n) & Dosing Schedule	Patient Characteristics	Outcomes	Harms
Factor VIII						
Manco-Johnson 2013[46] **Manco-Johnson 2013** **Manco-Johnson 2017**[45] ***SPINART***	Phase IIIb/IV randomized, controlled, parallel-group, open-label study Follow-up: 3 years	**Inclusion** -Males -Age 12 to 50 (aged 18-50 in Bulgaria and Romania) -Severe hemophilia A -No FVIII inhibitor status or history	1) Factor VIII prophylaxis 25 IU/kg 3 times weekly. Dose may be increased by 5 IU/kg at the end of year 1 and end of year 2 toa maximum dose of 30 or 35 IU kg	**Median Age (Range)** 1) 29.0 (15-50) 2) 29.0 (17-48) **Factor VIII Level <1%, n (%)** 1) 39 (92.9%) 2) 42 (100%)	**ABR Treated Bleeds (SD)** 70 Weeks 1) 2.2 (5.1) 2) 36.9 (23.8) 156 Weeks 1) 2.5 (4.7) 2) 37.2 (19.9)	**Any AE** 1) 59.5% 2) 88.1% **Serious AE** 1) 21.4% 2) 28.6%

Author & Year of Publication (Trial) Quality Rating	Study Design and Duration of Follow-up	Inclusion and Exclusion Criteria	Interventions (n) & Dosing Schedule	Patient Characteristics	Outcomes	Harms
Good quality		-6 to 24 documented bleeding events or treatments in past 6 months **Exclusions:** -Bleeding disorders other than Hemophilia A -Thrombocytopenia (defined as platelet count <100,000mm^{-3}) -Abnormal renal function -Active hepatic disease -Use of immunomodulating agents in last 3 months	2) Factor VIII on-demand dosing per investigator's clinical recommendation	**Presence of Target Joints, yes n (%)** 1) 28 (66.7%) 2) 31 (73.8%) **Median Bleeding Episodes in Last 6 Months (Range)** 1) 9.0 (2-23) 2) 12.0 (6-24) **Median Bleeding Episodes in Last 12 Months (Range)** 1) 17.0 (6-42) 2) 19.5 (8-47)	**ABR Treated Joint Bleeds (SD)** 70 Weeks 1) 1.9 (4.7) 2) 29.2 (20.6) 156 Weeks 1) 1.9 (4.1) 2) 28.7 (18.8) **Quality of life Haem-A-QoL changes from BL (95% CI)** 1) +3.98 points (-1.14 to +9.10; median: 4.40) 2) -6.00 points (-11.62 to -0.38; median: 0.27) Treatment Difference): 9.98 points (3.42 to 16.54, p=0.0034) favoring prophylaxis	**Treatment-Related AE** 1) 0% 2) 0%

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

Supplemental NMA Information

Table D3. NMA Feasibility Assessment

Trial	Study design	Study Duration	Interventions	Number of patients	Median age, years	Range age, years	Primary outcome assessed based on definition	NMA decision Include or Exclude
HAVEN 3[33] (Emicizumab)	Open label, randomized, multicenter trial	At least 6 months	Emicizumab 1.5 mg QW	36	36.5	19-77	Treated bleed	Include
			Emicizumab 3mg Q2W	35	41	20-65		
			On-demand FVIII	18	40	16-57		
SPINART[45,46] (Kogenate) [Manco-Johnson 2013 and Manco-Johnson 2017]	Open label, randomized, multicenter trial	3 years	FVIII Prophylaxis	42	29	17-48	Treated bleed	Include
			On-demand FVIII	42	29	17-50		
LEOPOLD 2 (Kovaltry) [Kavakli 2015][42]	Open-label, randomized crossover, multicenter trial	6 months each phase	FVIII Prophylaxis 2/wk	28	27	14-54	All bleeds	Exclude (see Table D4 below)
			FVIII Prophylaxis 3/wk	31	28	14-59		
			On-demand FVIII	21	30	14-53		
A-LONG (EloctateV)[43] [Mahlangu 2014]	Open-label, partially randomized, multicenter trial	Median: 28 weeks	Individualized Prophylaxis	118	29	16-65	Treated bleeds	Exclude (see Table D4 below)
			Weekly Prophylaxis	24	31.5	18-59		
			On-demand FVIII	23	34	13-62		
ESPRIT[44] [Gringerii 2011]	Open-label, randomized, pragmatic multicenter trial	10 years	FVIII Prophylaxis 3/wk	21	4.1	1– 7	Treated bleeds	Exclude (see Table D4 below)

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

Trials	Reasons for not including in NMA
LEOPOLD 2 (Kovaltry)[42] [Kavakli 2014]	**Outcome definition:** This study defined bleeding event as spontaneous bleeds, trauma-related bleeds, **untreated bleeds**, and unspecified events for which treatment was administered. As such a determination was made that the study reported 'all bleeding events' (and not treated bleeds that was the main outcome for the NMA). To further support this, the means of the annual bleeding rates in what would be the common comparator arms in the NMA (no prophylaxis arms) were vastly different from treated bleeds in HAVEN 3 (LEOPOLD 2: 57.5 versus HAVEN 3: 38.3).
A-LONG (EloctateV)[43] [Mahlangu 2014]	**Study design:** A-LONG was a partially randomized trial. The non-randomized arm of the study was for patients continuing factor VIII prophylaxis (EloctateV) at the FDA recommended dose (25-56 IU/KG at a dosing interval of 3-5 days). The randomized part of the study included no prophylaxis arm and weekly factor VIII prophylaxis, which is less frequent than the FDA recommended dose (25-56 IU/KG every 3-5 days). The authors noted that the factor VIII prophylaxis randomized arm was designed to provide efficacy data to inform decision for patients unwilling to comply with the recommended dose.
ESPRIT[44] [Gringerii 2011]	**Inclusion Criteria:** Conducted in children aged 1 to 7 years

Supplemental NMA Methods

As described in the report, all NMAs were conducted in a Bayesian framework using the gemtc package in R.[32] An NMA extends pairwise meta-analyses by simultaneously combining both the direct estimates (i.e., estimates obtained from head-to-head comparisons) and indirect estimates (i.e., estimates obtained from common comparator[s]).[84,85]

The outcomes (rates of treated bleeding events and rates of treated joint bleeding) were analyzed using a Poisson likelihood and the log link function. The primary inputs to the NMA were the number of bleeding events and the treatment exposure time in person-years. We included two studies in our NMA: HAVEN 3 and SPINART. Data on number of bleeding events and person-years of follow-up was not reported in HAVEN 3 trial. However, these inputs were obtained from Reye 2019 (a published NMA funded by the manufacturer of emicizumab).[86] Number of treated bleeding events was reported in SPINART; we estimated the person-years of follow-up in SPINART by the treatment duration multiplied by the number of participants in the trial.

For our primary results, we used a random-effects model. We expected a priori that the random-effects model would be more appropriate because of the potential differences in populations studied. The amount of between-study variance (i.e., heterogeneity) could not be accurately estimated due to the small number of studies available. Instead, based on evidence from prior study,[86] we used informative prior for the between-study deviation is $\tau \sim$Uniform (0,0.5), which corresponds to a 'range' of treatment effects (RRs) on the multiplicative scale of ~7.10. The deviance information criteria (DIC) and residual deviance (resdev) statistics were similar for the fixed and random effects models.

Figure D.1. Network Diagram

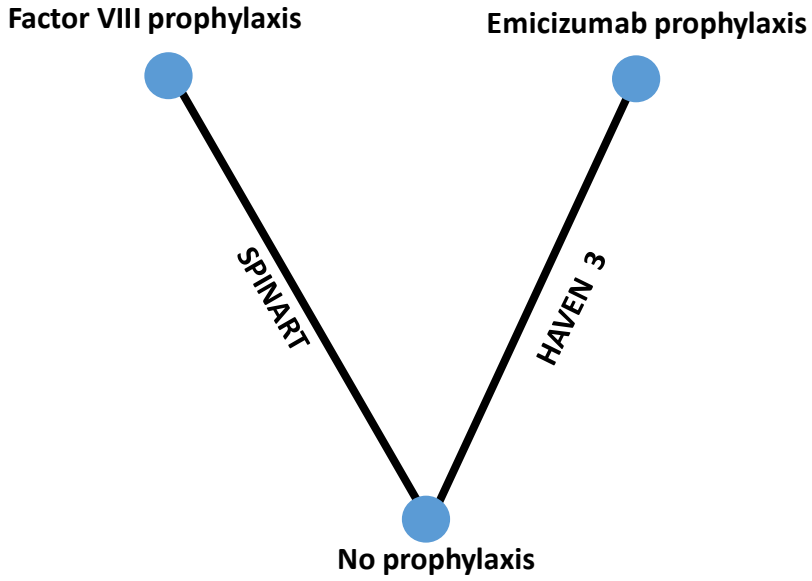


Table D5. NMA Data Inputs for Treated Bleeding Events

Study	Arm	Number of bleeds	Exposure (person-years)
HAVEN 3[33]	Emicizumab QW*	37	22.1
HAVEN 3[33]	Emicizumab Q2W*	32	22.3
HAVEN 3[33]	On-demand FVIII	369	8.18
SPINART[45,46]	FVIII prophylaxis	264	127.44
SPINART[45,46]	On-demand FVIII	4338	126.58

QW: Once weekly dosing

Q2W: Every 2 weeks

* The two emicizumab arms were combined in the NMA

Table D6. NMA Data Inputs for Treated Joint Bleeding Events

Study	Arm	Number of bleeds	Exposure (person-years)
HAVEN 3[33]	Emicizumab QW*	23	22.1
HAVEN 3[33]	Emicizumab Q2W*	19	22.3
HAVEN 3[33]	On-demand FVIII	220	8.18
SPINART[45,46]	FVIII prophylaxis	242	127.44
SPINART[45,46]	On-demand FVIII	3632	126.58

QW: Once weekly dosing

Q2W: Every 2 weeks

* The two emicizumab arms were combined in the NMA

Supplemental NMA Results (Fixed Effect NMA)

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

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

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

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

Appendix E. Comparative Value Supplemental Information

Table E.1. 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 [87]

Table E.2. List of Varied Parameters and Respective Distribution, Mean, and Standard Error

Parameter	Mean Input Value	SE	Distribution
Discount Rate	3.00%	1.28%	Beta
Bleed to Pettersson Score Conversion (Age ≥ 25)	6.520	0.130	Log Normal
Bleed to Pettersson Score Conversion (Age < 25)	36.520	0.130	Log Normal
Proportion of Joint Bleeds to Total Bleeds	0.660	0.084	Beta
Emicizumab Total Bleeds	2.600	0.130	Log Normal
Emicizumab Total Treated Bleeds	1.300	0.130	Log Normal
Emicizumab Treated Target Joint Bleeds	0.700	0.130	Log Normal
Emicizumab Treated Joint Bleeds	0.900	0.369	Log Normal
		-	-
NMA Fixed Effects Total Treated Bleeds RR (Emicizumab vs. Factor VIII)	0.570	0.190	Log Normal
NMA Fixed Effects Total Treated Joint Bleeds RR (Emicizumab vs. Factor VIII)	0.530	0.240	Log Normal
Valoctocogene Year 1 Factor VIII Level	64.290	0.130	Log Normal
Treated Joint Bleed RR (Valoctocogene vs Factor VIII)	0.092	0.294	Log Normal
Child All Bleeds RR	0.273	0.130	Log Normal
Child Treated Bleeds RR	0.069	0.130	Log Normal
Average Number of Blood Days	4.500	0.496	Log Normal
Proportion of Patients Switching FVIII Range 1	1.000	0.064	Beta
Proportion of Patients Switching FVIII Range 5	0.050	0.006	Beta
Patient Weight Age 0	5.400	0.100	Normal
Patient Weight Age 0.25	7.300	0.120	Normal
Patient Weight Age 0.5	8.500	0.120	Normal
Patient Weight Age 0.75	9.700	0.160	Normal
Patient Weight Age 1	11.400	0.100	Normal
Patient Weight Age 2	14.200	0.140	Normal
Patient Weight Age 3	16.000	0.160	Normal
Patient Weight Age 4	18.500	0.180	Normal
Patient Weight Age 5	21.200	0.390	Normal
Patient Weight Age 6	23.900	0.390	Normal
Patient Weight Age 7	28.100	0.520	Normal
Patient Weight Age 8	31.500	0.580	Normal
Patient Weight Age 9	33.800	0.690	Normal
Patient Weight Age 10	40.300	1.250	Normal
Patient Weight Age 11	48.500	1.390	Normal
Patient Weight Age 12	50.600	1.440	Normal
Patient Weight Age 13	60.700	1.640	Normal
Patient Weight Age 14	65.900	1.830	Normal
Patient Weight Age 15	71.300	1.910	Normal
Patient Weight Age 16	74.400	1.210	Normal
Patient Weight Age 17	75.100	2.080	Normal
Patient Weight Age 18	81.400	3.220	Normal

Parameter	Mean Input Value	SE	Distribution
Patient Weight Age 19	78.900	2.240	Normal
Patient Weight Age 20	84.700	1.180	Normal
Patient Weight Age 30	90.200	0.780	Normal
Patient Weight Age 40	91.500	0.730	Normal
Patient Weight Age 50	90.500	0.920	Normal
Patient Weight Age 60	90.600	1.370	Normal
Patient Weight Age 70	85.800	0.920	Normal
Patient Weight Age 80	79.200	0.860	Normal
Advate (F8) Factor VIII Prophylaxis Distribution	71.15%	0.130	Dirichlet
Eloctate (F8) Factor VIII Prophylaxis Distribution	28.85%	0.130	Dirichlet
Advate (F8) Net Drug Cost	$1.14	$0.13	Log Normal
Eloctate (F8) Net Drug Cost	$1.93	$0.13	Log Normal
Emicizumab Net Drug Cost	$95.03	$0.13	Log Normal
Valoctocogene Net Drug Cost	$2,500,000	$0.13	Log Normal
Advate (F8) Furnishing Discount (%)	6.00%	0.77%	Beta
Eloctate (F8) Furnishing Discount (%)	6.00%	0.77%	Beta
Emicizumab Furnishing Discount (%)	6.00%	0.77%	Beta
Valoctocogene Furnishing Discount (%)	0.00%	0.00%	Beta
Advate (F8) Prophylaxis Drug Dosing	105.000	0.000	Normal
Eloctate (F8) Prophylaxis Drug Dosing	78.000	0.000	Normal
Advate (F8) Factor VIII On Demand Distribution	0.712	0.130	Dirichlet
Eloctate (F8) Factor VIII On Demand Distribution	0.288	0.130	Dirichlet
Advate (F8) On Demand Drug Dosing	50.400	6.429	Normal
Eloctate (F8) On Demand Drug Dosing	50.400	6.429	Normal
Cost/Bleed Age ≤ 18	$765.48	$0.13	Log Normal
Cost/Bleed 18 < Age ≤ 45	$4,604.32	$0.13	Log Normal
Cost/Bleed Age > 45	$6,858.24	$0.13	Log Normal
Surgery Costs	$44,747.17	$0.13	Log Normal
No Arthropathy Outpatient Physician Visit Rate	4.145	0.130	Log Normal
No Arthropathy Outpatient Nurse Visit Rate	2.540	0.130	Log Normal
No Arthropathy X-Ray Rate	0.485	0.130	Log Normal
No Arthropathy Computed Romography Rate	0.125	0.130	Log Normal
No Arthropathy Magnetic Resonance Imaging Rate	0.125	0.130	Log Normal
No Arthropathy Ultrasonography Rate	0.205	0.130	Log Normal
Arthropathy Outpatient Physician Visit Rate	6.630	0.130	Log Normal
Arthropathy Outpatient Nurse Visit Rate	3.840	0.130	Log Normal
Arthropathy X-Ray Rate	1.145	0.130	Log Normal
Arthropathy Computed Romography Rate	0.240	0.130	Log Normal
Arthropathy Magnetic Resonance Imaging Rate	0.260	0.130	Log Normal
Arthropathy Ultrasonography Rate	0.500	0.130	Log Normal
Outpatient Physician Visit Cost per Resource Use	$45.77	$0.13	Log Normal
Outpatient Nurse Visit Cost per Resource Use	$23.07	$0.13	Log Normal

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

Table E3. Undiscounted Outcomes for the Base Case Models

Treatment	Drug Cost	Total Cost	Joint Bleeds	Treated Non-Target Joint Bleeds	Treated Target Joint Bleeds	Life Years	QALYs
Factor VIII (Model version 1 – Health Sector Perspective)	$27,471,000	$29,097,000	196.92	63.57	69.20	58.22	38.56
Valoctocogene Roxaparvovec (Model version 1 – Health Sector Perspective)	$31,804,000	$32,755,000	99.72	34.86	40.65	58.22	38.72
Factor VIII (Model version 1 – Modified Societal Perspective)	$27,471,000	$29,251,000	196.92	63.57	69.20	58.22	38.56
Valoctocogene Roxaparvovec (Model version 1 – Modified Societal Perspective)	$31,804,000	$32,843,000	99.72	34.86	40.65	58.22	38.72
Factor VIII (Model version 2 – Health Sector Perspective)	$31,100,000	$32,790,000	228.48	71.68	75.97	75.08	54.62
Emicizumab (Model version 2 – Health Sector Perspective)	$40,632,000	$41,627,000	115.27	39.26	44.64	75.08	55.21

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

Figure E.1. Tornado Diagrams for Model Version 2: Emicizumab vs Factor VIII Incremental Societal Costs

Parameter	Low Input Value	High Input Value
Pettersson 1-12 Utilities (Age ≤ 30)	0.62	1.00
Pettersson 0 Utilities (Age ≤ 30)	0.71	1.00
NMA Fixed Effects Total Treated Joint Bleeds RR	0.32	0.82
NMA Fixed Effects Total Treated Bleeds RR	0.39	0.82
Pettersson 1-12 Utilities (Age > 60)	0.41	0.68
Pettersson 13-21 Utilities (Age > 60)	0.41	0.68
Pettersson 0 Utilities (30 < Age ≤ 40)	0.63	1.00
Pettersson 1-12 Utilities (30 < Age ≤ 40)	0.56	0.93
Average Number of Blood Days	1.00	7.00
Emicizimuab Treated Joint Bleeds	0.40	1.70

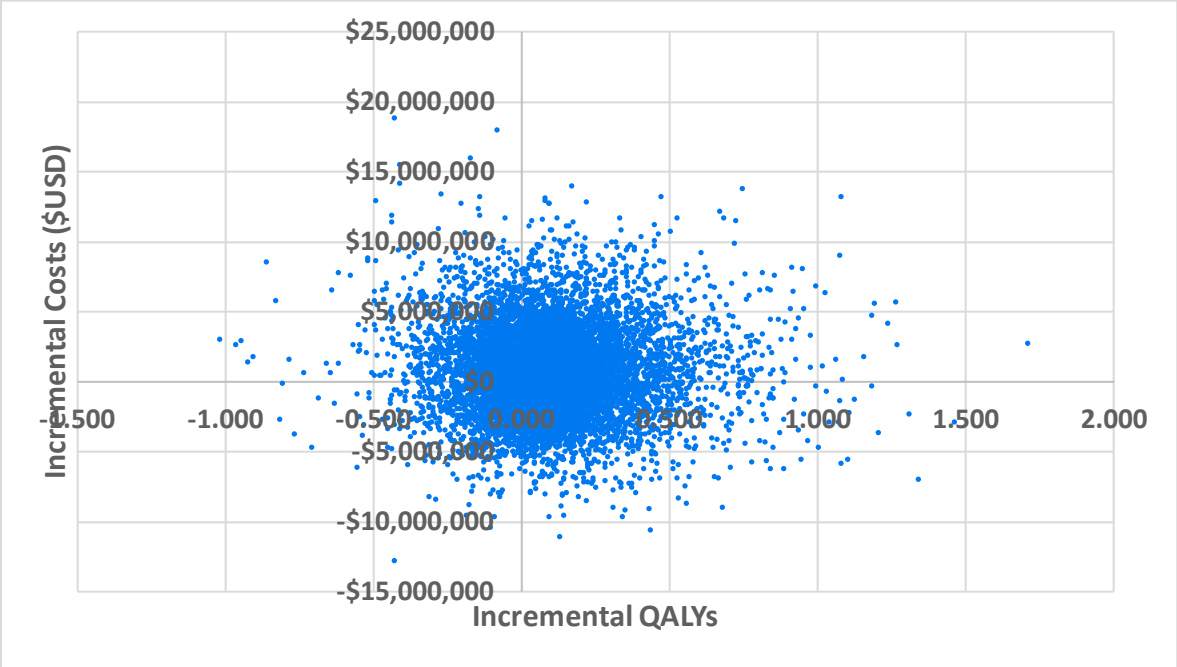
Table E.4. Results of Probabilistic Sensitivity Analysis for Valoctocogene Roxaparvovec and Emicizumab versus Factor VIII

	Valoctocogene/Emicizumab		Factor VIII		Incremental	
	Mean	Credible Range	Mean	Credible Range	Mean	Credible Range
Model version 1 – Health Sector Perspective						
Total Costs	$14,775,042	[$7,931,241, $23,501,613]	$14,123,388	[$8,102,856, $21,566,308]	$631,655	[-$3,961,611 $5,892,697]
Total QALYs	19.92	[12.55, 28.17]	19.83	[12.50, 28.01]	0.094	[-0.217, 0.459]
ICER	-	-	-	-	-$3,056,804	[-$95,806,229, $105,245,771]
Model version 1 – Modified Societal Perspective						
Total Costs	$14,798,858	[$7,958,852, $23,569,441]	$14,200,975	[$8,153,095, $21,677,785]	$587,833	[-$4,008,339 $5,851,908]
Total QALYs	19.92	[12.55, 28.17]	19.83	[12.50, 28.01]	0.094	[-0.217, 0.459]
ICER	-	-	-	-	-$2,518,273	[$-$95,499,246 $104,914,823]
Model version 2 – Health Sector Perspective						
Total Costs	$15,111,067	[$6,592,249, $26,675,194]	$11,847,929	[$5,06416 , $20,576,832]	$3,263,137	[-$1,473,124, $9,668,888]
Total QALYs	25.55	[15.37, 37.41]	25.24	[15,17, 36.99]	0.307	[-0.084, 0.849]
ICER	-	-	-	-	$37,779,682	[-$30,799,818, $68,347,234]

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

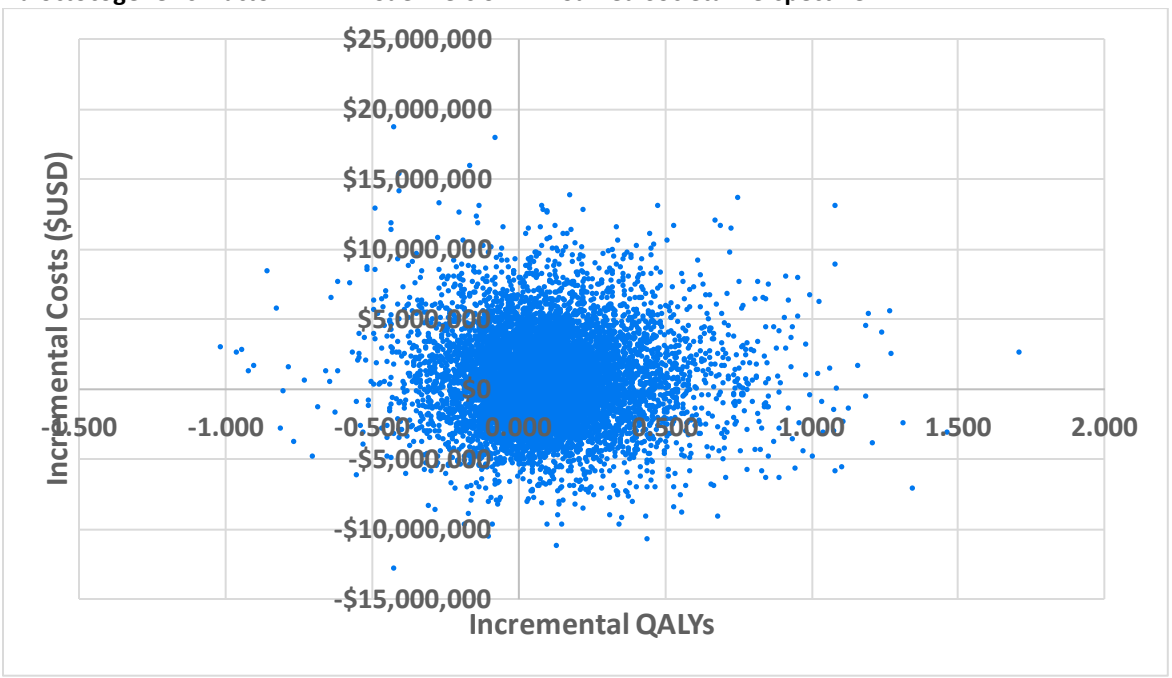
Figure E.2. Probabilistic Sensitivity Analysis Results: Cost-Effectiveness Planes

Valoctocogene vs. Factor VIII – Model Version 1 Health Sector Perspective



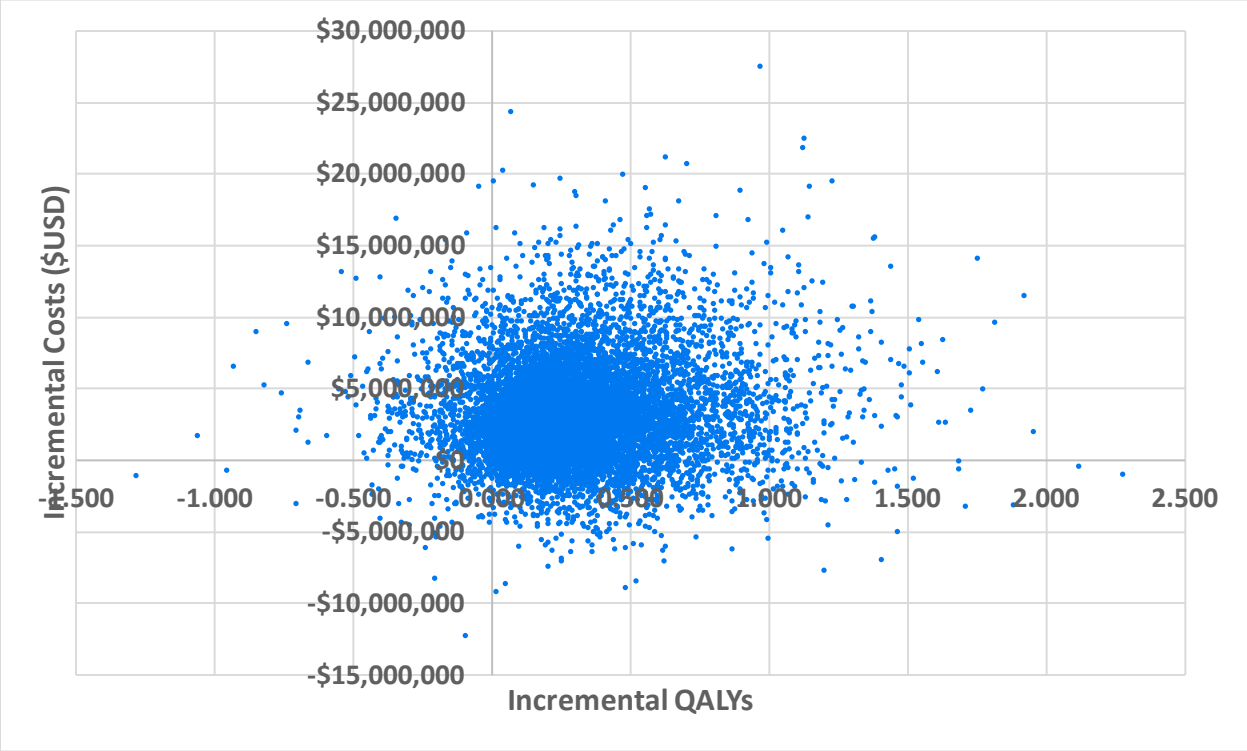
Results use a placeholder price of $2,500,000 for valoctocogene roxaparvovec

Valoctocogene vs. Factor VIII – Model Version 1 Modified Societal Perspective



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

Emicizumab vs. Factor VIII – Model Version 2 Health Sector Perspective



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