# Gene Therapy for Hemophilia B and an Update on Gene Therapy for Hemophilia A

**Draft Background and Scope**

**May 5, 2022**

## Background

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

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

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

The severity of hemophilia A and B has generally been defined by factor levels (the percentage of normal factor that a patient has).[3] Severity based on factor levels does not perfectly correlate with any individual's clinical severity, but no other classification system is widely accepted.[4] Using factor level classifications, severe disease is defined by factor levels below 1% of normal.[3] 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.[5] Patients with moderate disease (factor levels of 1% to 5% of normal) typically have delayed bleeding episodes after minor trauma several times per year, but only occasionally have spontaneous

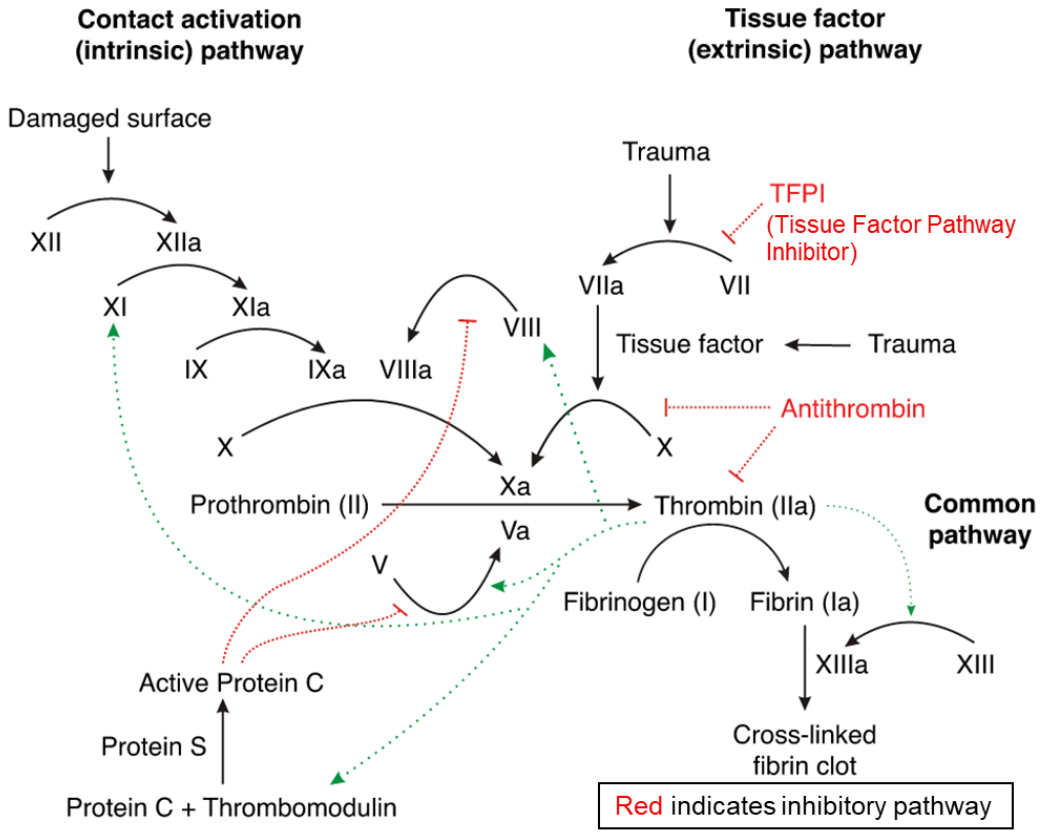
bleeding.[6] Individuals with mild disease (factor levels between 5% to 40% of normal) typically have bleeding after procedures such as tooth extractions or surgery, or after significant injuries.[6]

To reduce the risk of bleeding, patients with severe hemophilia have typically administered factor concentrate intravenously several times each week.[6,7] The use of factor concentrates both as treatment and prophylaxis, has dramatically altered the management and clinical course of patients with hemophilia. However, prophylaxis with factor replacement is burdensome and does not maintain patients at normal levels of factor. Several factor preparations are available for prophylaxis, some with modifications to extend the half-life of the therapy, some prepared from human plasma, and some prepared using recombinant technology. Many patients with hemophilia A now use emicizumab, a monoclonal antibody that can be administered monthly by subcutaneous injection, for prophylaxis in preference to factor VIII; no similar treatment is currently available for hemophilia B.

Valoctocogene roxaparvovec is an adeno-associated virus serotype 5 (AAV5) mediated gene therapy for hemophilia A.[8] It delivers a B-domain-deleted gene to cells in the liver, resulting in production of an active variant of factor VIII. In August 2020, BioMarin Pharmaceutical received a complete response letter from the FDA changing the primary endpoint of the pivotal trial to the annualized bleeding rate at two years in the Phase 3 trial. The last patient in the trial completed two years of follow-up in November 2021.

Etranacogene dezaparvovec is an AAV5-mediated gene therapy for hemophilia B. It delivers the Padua variant of the gene for factor IX to cells in the liver, resulting in production of an active variant of factor IX. UniQure with CSL Behring is expected to submit its biologic license application to the FDA in the first half of 2022 with an expected FDA decision in late 2022 or early 2023.

**Figure 1. Illustration of Activated Factor VIII and Factor IX 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.

## Stakeholder Input

This draft scoping document was developed with input from diverse stakeholders, including patients and their families, clinicians, researchers, and manufacturers of the agents of focus in this review. This document incorporates feedback gathered during preliminary calls with stakeholders and open input submissions from the public. A revised scoping document will be posted following a three-week public comment period. ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of preventive treatments.

One overarching theme we heard was that the outcome that matters most to patients is participation. This includes participation in family life, recreational activities, school activities, and work activities without restriction. This reflects both the impact of bleeding events on time away from activities and the fear of bleeding events limiting participation.

Bleeding events and joint pain are important, but the sequelae of those outcomes are equally important. Living with uncertainty and chronic pain can lead to significant mental health issues (anxiety, depression, fatigue, substance use issues). The psychosocial impact of hemophilia on patients and their caregivers is enormous.

Intravenous infusions are an enormous burden to patients and to their caregivers. A huge weight would be lifted if regular factor infusions were no longer required.

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

We also heard that patients are reluctant to try new therapies. The hemophilia community has been harmed in the past by heralded new therapies that turned out to be disastrous. Once they achieve stability on with a specific therapy, they are loathe to change even if there are theoretical benefits to a novel therapy (fewer infusions, subcutaneous rather than IV administration). The community understands the need for substantial numbers of patients followed for a long time to ensure that the benefits outweigh potential unknown harms. They are particularly concerned about the durability of gene therapy and potentially wasting what could be one shot at gene therapy on an approach that ends up not having lifetime efficacy. They are also concerned about the potential for thrombotic events.

## Report Aim

This project will evaluate the clinical and economic outcomes of valoctocogene roxaparvovec for patients with hemophilia A and etranacogene dezaparvovec for hemophilia B. The ICER value framework includes both quantitative and qualitative comparisons to ensure that the full range of benefits and harms – including those not typically captured in the clinical evidence such as public health effects, reduction in disparities, innovation, and patient experience – are considered in the judgments about the clinical and economic value of the interventions.

## Applicable Framework Adaptations

We propose to assess both valoctocogene roxaparvovec and etranacogene dezaparvovec under an adaptation of the ICER Value Framework for treatments of serious, ultra-rare conditions because we believe they meet the following criteria:

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

There are estimated to be approximately 24,000 individuals with hemophilia A in the US.[9] Valoctocogene roxaparvovec is intended for the treatment of adults with severe hemophilia A. Approximately 60% of patients with hemophilia A have severe disease and many will not be eligible for valoctocogene roxaparvovec because of age or comorbidities, so we estimate that the eligible population will be below 10,000 individuals. As such, valoctocogene roxaparvovec is a therapy for an ultra-rare condition.

There are estimated to be approximately 6,000 individuals with hemophilia B in the US.[9] Etranacogene dezaparvovec is intended for the treatment of adults with severe hemophilia B, so the eligible population will be well below 10,000 individuals. As such, etranacogene dezaparvovec is a therapy for an ultra-rare condition.

We also propose to assess both valoctocogene roxaparvovec and etranacogene dezaparvovec under an adaptation of the ICER Value Framework for treatments of high-impact "single and short-term therapies" (SSTs), because we believe they meet the following criteria defined as:

- The therapy is delivered through a single intervention or a short-term course (less than one year) of treatment that offers a significant potential for substantial and sustained health benefits extending throughout patients' lifetimes.
- The therapy can eradicate a disease or condition or produce sustained major health gains that can halt the progression of significant illnesses.

Valoctocogene roxaparvovec is a one-time gene therapy for hemophilia A, a prototypical example of an SST, and will be evaluated under this framework. Similarly, etranacogene dezaparvovec is a one-time gene therapy for hemophilia B and will be evaluated under this framework

Following formal public comment and discussions with stakeholders, ICER will make a final decision on whether the therapy meets these criteria and will be assessed using an adapted approach.

## Scope of Clinical Evidence Review

The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be collected from randomized controlled trials as well as high-quality systematic reviews; observational studies and case series will be considered for inclusion as well, given the limited evidence base for valoctocogene roxaparvovec for hemophilia A and etranacogene dezaparvovec for hemophilia B. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see ICER's grey literature policy).

Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided in a forthcoming Research Protocol to be published on the Open Science Framework website (https://osf.io/7awvd/).

### *Populations*

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

### *Interventions*

The interventions of interest for this review are listed below:

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

### *Comparators*

Data permitting, we intend to compare the interventions to prophylaxis with factor preparations and, in the case of valoctocogene roxaparvovec, to emicizumab. We will compare etranacogene dezaparvovec to prophylaxis using factor IX preparations. The reviews of the interventions for hemophilia A and hemophilia B will be considered separately.

### *Outcomes*

Patients and patient groups directed us to review the core outcome set established through coreHEM, an international multi-stakeholder project that convened 49 experts (patients, clinicians, researchers, drug developers, methodologists, regulators, health technology assessors and payers) to identify a core set of outcomes for hemophilia gene therapy trials.[10] Specifically, the coreHEM project identified six core outcomes as crucial for evaluating the effectiveness of gene therapy: frequency of bleeds, factor activity level, duration of expression, chronic pain, mental health status, and utilization of the healthcare system (direct costs).[10] The coreHEM outcomes have been integrated in our outcome list below.

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

- Patient Important Outcomes:
    - Patient-reported quality of life
    - Rates of bleeding events
    - Rates of treated bleeding events
    - Rates of treated joint bleeding and treated target joint bleeding
    - Pain (chronic and acute)
    - Mental health status
    - Burdens of therapy
    - Mortality
    - Adverse events including:
        - Thrombosis
        - Liver toxicity
- Other Outcomes:
    - Factor level (factor activity level)
    - Duration of expression of the clotting factor gene
    - Utilization of healthcare system
    - Adverse events including:
        - Immune response to factor (Inhibitor development)
        - Immune response to gene therapy

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

We will also look 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.

***Timing***

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

***Settings***

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

## 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. These general elements (i.e., not specific to a given disease) are listed in the table below.

**Table 1.2. Categories of Contextual Considerations and Potential Other Benefits or Disadvantages**

| **Contextual Consideration*** |
|---|
| Acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability |
| Magnitude of the lifetime impact on individual patients of the condition being treated |
| Other (as relevant) |

*Contextual considerations refer to social or ethical priorities that shape to some extent how the value of any effective treatments for a particular condition will be judged.

| **Potential Other Benefit or Disadvantage*** |
|---|
| Patients' ability to achieve major life goals related to education, work, or family life |
| Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life |
| Patients' ability to manage and sustain treatment given the complexity of regimen |
| Society's goal of reducing health inequities |
| Other (as relevant) |

*Potential other benefits or disadvantages are meant to reflect the broader effects of a specific treatment on patients, caregivers, and society.

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

## Scope of Comparative Value Analyses

As a complement to the evidence review, we will update our prior simulation model and corresponding assessment of the cost-effectiveness of using valoctocogene roxaparvovec versus prophylaxis using emicizumab and prophylaxis using factor VIII preparations. We will also adapt that model to assess, separately, the cost effectiveness of etranacogene dezaparvovec relative to prophylaxis using factor IX for hemophilia B. A detailed economic model analysis plan with proposed methodology, model structure, parameters, and assumptions is forthcoming. At this time, we anticipate that the model structure for hemophilia B will closely resemble the prior model for hemophilia A, developed itself based on prior models and available evidence, but with updated

key model inputs based on an updated literature review and communications with stakeholder as well as evidence from clinical trials and observational studies of hemophilia A and B treatments.[11-13]

The population entering the models will consist of patients without inhibitors requiring prophylaxis for hemophilia A and separately for hemophilia B. The proposed models will consider four mutually exclusive bleed states, including: 1) no bleed (origination state), 2) untreated bleed, 3) treated bleeds not into a target joint, 4) treated target-joint bleed, and death as the absorbing state. In addition, the models will consider the lifetime risk and consequences of arthropathy. The model will be developed from a health-care system perspective over a lifetime time horizon. In addition, a modified societal perspective will be explored in a scenario analysis, as data allow. This modified societal perspective analysis will be considered as a co-base case if the societal costs of care are large relative to direct health care costs, and the impact of treatment on these costs is substantial. This will most often occur in cases where the incremental cost-effectiveness ratio changes by greater than 20%, greater than $200,000 per quality-adjusted life years (QALY), and/or when the result crosses the threshold of $100,000-$150,000 per QALY gained.

Data permitting, key inputs for the hemophilia A and B models will include the relevant transition rates for each health state (e.g., treated and untreated bleed rates, arthropathy rates, symptom improvement, mortality), treatment-related adverse events and health utilities. Model cost inputs will include those of the prophylaxis and treatment regimens, non-drug costs, costs of treating adverse events, and costs of ongoing care that are essential to the current paradigm of treatment. Data permitting, sub-group scenario analyses varying patient age and factor level upon initiation of therapy will be constructed. Results from the model will include the estimated mean life expectancy, quality-adjusted life expectancy, equal-value life expectancy, health outcomes such as number of additional bleeds prevented, and health care costs. These results will be used to estimate the incremental cost per bleed prevented and the incremental cost per life-year gained, per equal value life-year (evLY) gained, and per quality-adjusted life-year (QALY) gained. Further, the ultra-rare and SST frameworks will be followed which will include several specified scenario analyses.

In separate analyses, we will explore the potential health system budgetary impact of treating hemophilia A patients in need of prophylaxis with valoctocogene roxaparvovec over a five-year time horizon, utilizing published or otherwise publicly available information on the potential population eligible for treatment and results from the simulation model for treatment costs and cost offsets. This potential budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact, and will allow assessment of the potential for needing to manage the cost of the intervention. We will also conduct these analyses for hemophilia B patients requiring prophylaxis with etranacogene dezaparvovec. More information on ICER's methods for estimating potential budget impact can be found here.

***Identification of Low-Value Services***

Identification of Low-Value Services As described in its Final Value Assessment Framework, ICER will now include in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see ICER Value Framework). These services are not ones that would be directly affected by the gene therapy (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.

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