The value of INNOVATIVE MEDICINE

The clinical and economic impact of the first gene therapy for hemophilia B

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WITH INNOVATION COMES **CHANGE**

Innovative treatments like gene therapy bring with them the promise of improving lives and momentum in our industry's quest to advance modern medicine

At the same time, breakthrough treatments bring change to both clinical and health economic paradigms.

We would argue that solutions to potential challenges that accompany innovation require collaboration, communication, and alignment around how we define value.

Using CSL Behring's new gene therapy for hemophilia B as a case example, we hope to provide a construct for how we evaluate breakthrough treatments. We believe clinical benefit, cost impact, and appropriate patient selection should go hand in hand and be at the center of our conversations about value.

CSL Behring has been delivering biotechnology innovation and excellence for more than a century. Over the last 4 decades, CSL has played a leading role in advancing hemophilia care, including developing innovative recombinant factor VIII and IX products, improving treatment administration, and investing in gene therapy for hemophilia B.

Those efforts reached an historic milestone on June 19, 2023, when the first person with hemophilia B received the first commercialized single dose of CSL Behring's HEMGENIX® (etranacogene dezaparvovec-drlb).[1]

HEMGENIX is the first and only US Food and Drug Administration (FDA)–approved gene therapy for adults with hemophilia B who currently use factor IX prophylaxis therapy, or have current or historical life-threatening bleeding, or have repeated, serious spontaneous bleeding episodes.

Solutions to potential challenges that accompany innovation require collaboration, communication, and alignment around how we define value

Gene therapy represents cutting-edge medicine that is changing the lives of people with genetic conditions by addressing the root cause of their disease

Researchers have been studying gene therapy for more than 30 years and hemophilia B patients have been patiently waiting for this paradigm-shifting treatment to arrive.

"The excitement in the hemophilia B patient community over gene therapy is extraordinary and CSL is proud to be part of that story," said Debbie Bensen-Kennedy, MD, Vice President of Medical Affairs, North America, at CSL Behring. "It has been and will continue to be CSL's commitment to support people with rare disease, bring them innovative medicines, decrease the burden of their illness, and improve their lives."

With HEMGENIX, not only are the clinical benefits significant, but the potential savings to the healthcare system over time are substantial.

Indeed, novel treatments like HEMGENIX are easing the burden of illness for patients and adding value to the healthcare system by reducing medical spending over the long term.

In the following analysis, we'll review the value of HEMGENIX, which the Institute for Clinical and Economic Review (ICER) has projected to generate substantial cost savings and significant improvement in clinical outcomes.[2]

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UNDERSTANDING **HEMOPHILIA B**

Hemophilia B is a rare bleeding disorder that occurs in 5 per 100,000 male births[3,4]

It is caused by a defect in a gene encoding coagulation factor IX, which is expressed primarily in hepatocytes.[3,5] While hemophilia B is predominantly genetic in nature, nearly one-third of all mutations are spontaneous.[3,6]

Severe hemophilia B is characterized by frequent spontaneous and/or traumatic bleeding into joints, muscles, and internal organs, and can result in reduced life expectancy.[3,7,8]

People with hemophilia B who suffer recurrent bleeding increase their risk of[3,9-18]:

- **Long-term** inflammation and joint degeneration
- **Irreversible** joint damage
- **Hemophilic** arthropathy
- **Acute** and chronic pain

THE SEVERITY OF HEMOPHILIA B IS DEPENDENT ON NATIVE COAGULATION FACTOR ACTIVITY[6,19-21]

MILD	MODERATE	SEVERE
22.8% of hemophilia B patients	**37.5%** of hemophilia B patients	**39.1%** of hemophilia B patients
>5% to 40% FIX	**1% to 5% FIX**	**<1% FIX**

Abbreviation: FIX, factor IX.

Unmet clinical needs, despite a well-established standard of care

Treatment approaches for hemophilia B vary depending on its severity; however, intravenous (IV) infusion of purified or recombinant factor IX has been at the forefront of treatment for years.[3,10,22]

The therapeutic goal of replacement therapy is to reduce any spontaneous, breakthrough, or trauma-related bleeding, especially joint hemorrhages that could lead to arthropathy and disability.[3]

In terms of prevalence, 33,000 Americans have hemophilia.[23] Of those with hemophilia B, about 1,600 are on prophylactic factor IX therapy, with approximately 800 adults who could be appropriate candidates for HEMGENIX® (etranacogene dezaparvovec-drlb).[9,24]

That translates to about 2 to 3 members per every 1-million-member healthcare plan. As such, the appropriate patient population for HEMGENIX is relatively small.

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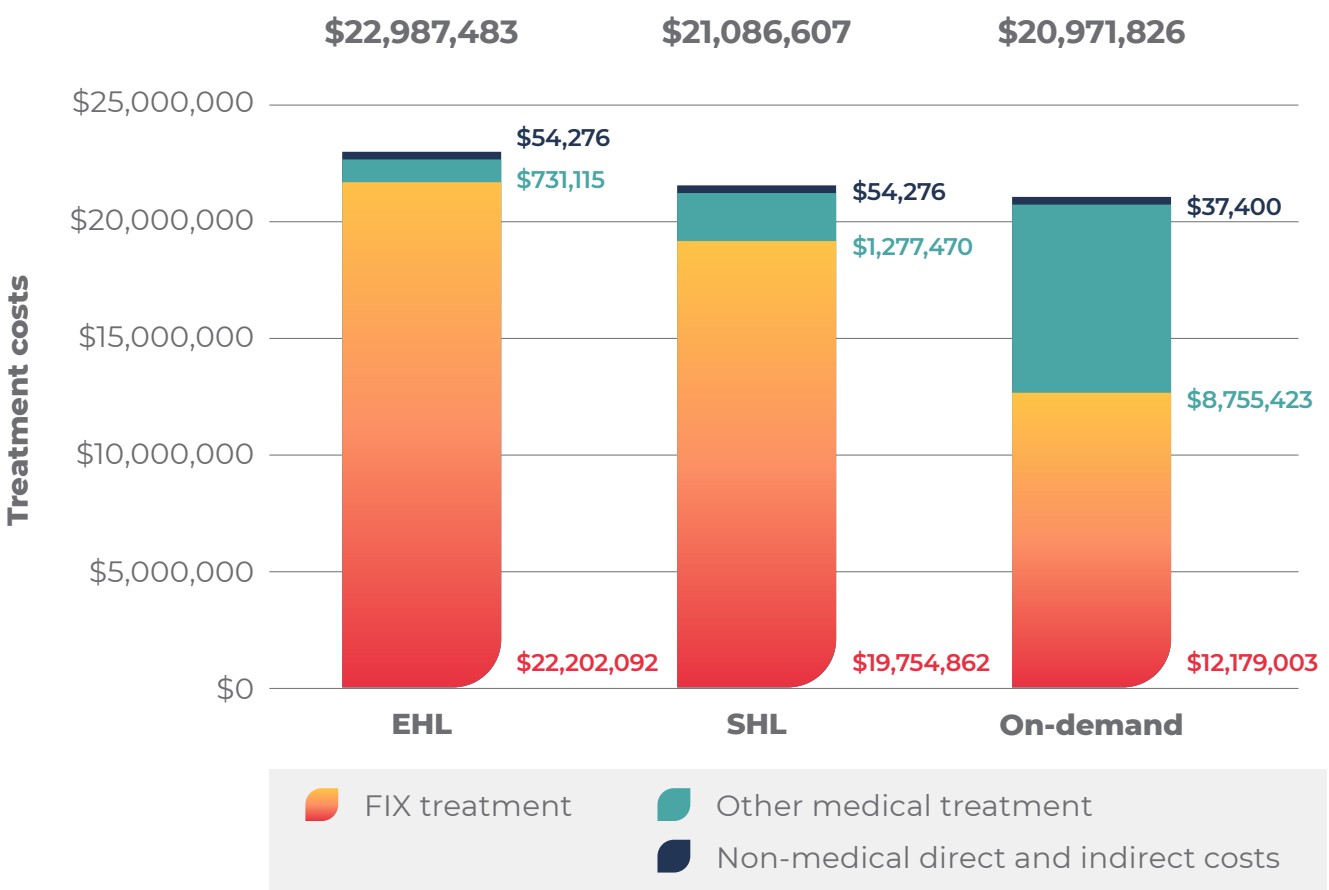
THE ECONOMIC BURDEN ASSOCIATED WITH **HEMOPHILIA B**

LIFELONG COST OF HEMOPHILIA B MANAGEMENT[25]

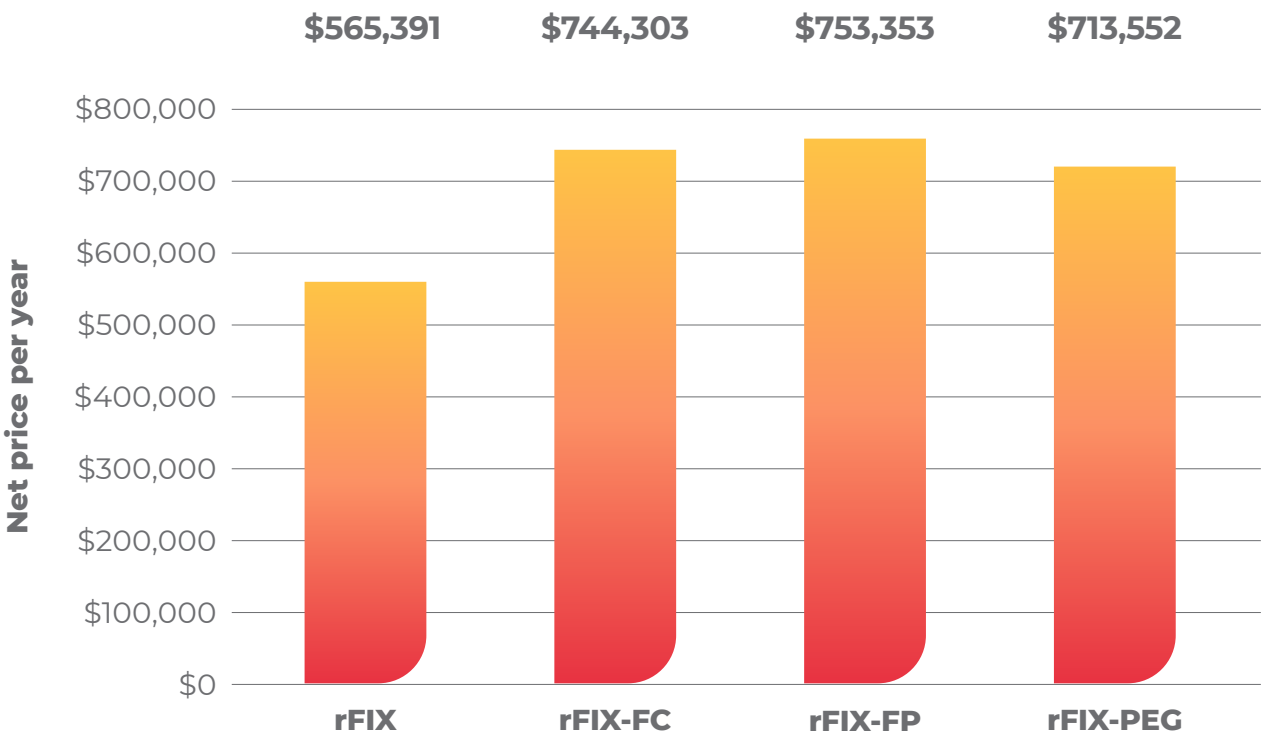


Abbreviations: EHL, extended half-life; FIX, factor IX; SHL, standard half-life.

The cost to treat a hemophilia B patient over their adult lifetime can easily exceed $20 million, with the vast majority of that cost coming from factor IX replacement therapy, according to a study published by Li et al.[25]

In a study of the economic burden associated with differing clinical profiles of hemophilia B, increasing disease severity was associated with increased management and medical costs.[26]

NET ANNUAL PRICE FOR PROPHYLACTIC FACTOR IX TREATMENT[2]



Abbreviations: FC, Fc fusion protein; FIX, factor IX; FP, albumin fusion protein; PEG, polyethylene glycol; r, recombinant.

Treatment-related healthcare costs were calculated based on the average sales price (ASP) of the drug per IU plus a 6% markup, per ICER's reference case that indicates a 6% markup should be included in populations receiving Part B drugs. Drug dosing costs were based on an 81.4-kg weight and most often used an IU/kg dose. Costs of drug per year are based on the weighted average of usual doses with weights of 32.26%, 32.26%, 33.33%, and 2.15% for rFIX, rFIX-FC, rFIX-FP, and rFIX-PEG, respectively.[2]

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BREAKING NEW GROUND TO ADDRESS **UNMET NEEDS**

As an inherited monogenic disease, hemophilia B is well suited for treatment with gene therapy because:

- **Manifestations** of the disease are caused by a single gene defect[26]
- **Small increases** in plasma levels of factor can meaningfully reduce symptoms of the disease[26]
- **The gene** cassette for factor IX is about 1.5 kb and easily packaged into a range of viral vectors[27]
- **Hepatocytes** are the native site of factor IX production[28]

HEMGENIX® (etranacogene dezaparvovec-drlb) is an adeno-associated virus serotype 5 (AAV5) gene therapy product that expresses a highly functional copy (the Padua variant) of the F9 gene.[29] With a single dose, HEMGENIX can help alleviate the burdens associated with the current standard of care treatment options.

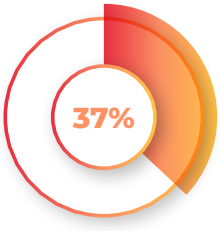
In fact, in the Health Outcomes with Padua gene; Evaluation in Hemophilia B (HOPE-B) phase 3 clinical trial, HEMGENIX was associated with sustained factor IX activity, with the mean factor IX level at 37% at 2 years, eliminating the peaks and troughs associated with factor IX prophylactic therapies.

For payers, a reduction in annualized bleed rate (ABR) with HEMGENIX compared with the standard of care, prophylactic factor IX, offers a cost offset. In clinical trials, HEMGENIX was safe and effective with no treatment-related serious adverse reactions and no development of factor IX inhibitors reported at 24 months.

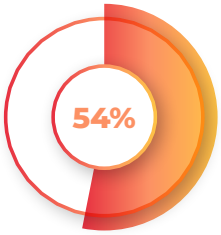
In their cost-effectiveness analysis, ICER projects HEMGENIX to be a "dominant" treatment compared with factor IX prophylaxis, with sustained factor IX levels for an estimated 23 years, according to their base-case analysis.[2]

This projection of 23 years of durability is further supported by a CSL-funded analysis published in 2022 by Shah et al, which used clinical trial data and a Bayesian model to predict that over 80% of patients would be free from prophylactic factor IX replacement therapy for 25.5 years post HEMGENIX infusion.[30] It's important to note that these are projections that will be validated or may change as real-world evidence becomes available.

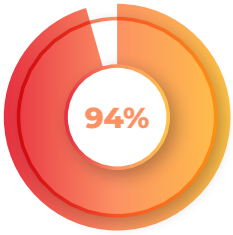
A SINGLE DOSE OF HEMGENIX WAS ASSOCIATED WITH[31]:



mean FIX activity sustained at 2 years



reduction in ABR compared with lead-in period*



of patients discontinued FIX prophylaxis and remained prophylaxis free†

Abbreviations: ABR, annualized bleed rate; FIX, factor IX.

*In a noninferiority study, the ABR for all bleeds decreased from an average of 4.1 for prophylaxis during the lead-in period to 1.9 in months 7 to 18 post treatment, an ABR ratio of 0.46 (95% CI, 0.26-0.81).

†Two patients were not able to stop routine prophylaxis. During months 7 to 18, an additional patient received prophylaxis during days 396 to 534 (approximately 20 weeks).

"HEMGENIX is an important addition to the current treatment paradigm and a long-awaited advancement for the treatment of hemophilia B"

As the HEMGENIX open-label extension trial continues, additional clinical data will be published as they are reported.

"HEMGENIX is an important addition to the current treatment paradigm and a long-awaited advancement for the treatment of hemophilia B," said Matthew Ryan, MD, adult hematologist and medical director at Hemophilia Outreach Center, Green Bay, Wisconsin, the site of the first HEMGENIX infusion.

"This exciting treatment offers patients a chance to live a life without frequent bleeds or the burden of regular infusions. The availability of this one-time treatment also sparks additional conversations when it comes to treatment options and goals, which is extremely important when managing a lifelong condition."

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MEASURING THE VALUE OF **INNOVATIVE MEDICINE**

Assessing the value of any treatment entails looking at the clinical benefits that it provides to patients as well as the cost impact it has on the healthcare system

The clinical value of HEMGENIX® (etranacogene dezaparvovec-drlb) is evidenced by its demonstrated ability to elevate and sustain factor IX levels for at least 2 years, significantly reduce the rate of annual bleeds versus the standard of care, and reduce the need for prophylactic treatment in 94% of people who received the therapy.

In addition to the potential long-term health benefits from greater bleed protection and freedom from infusion schedules, HEMGENIX can also generate significant cost savings for the healthcare system at large.

Specifically, healthcare costs can be 25 times higher for a person living with hemophilia B compared with an individual who does not have a bleeding disorder.[32] The average cost of prophylactic factor IX treatment for a patient with hemophilia B ranges from a low of $565,391 to a high of $753,353 per year, according to the ICER analysis.

With a cost of $3.5 million, HEMGENIX treatment would offer a break-even point for payers in about 4.6 to 6.2 years. Over the lifetime of a patient, ICER's base-case analysis forecasts net savings of more than $6 million for HEMGENIX relative to the standard of care.[2]

Working together to bring HEMGENIX to patients

As is the case with any paradigm-shifting treatment, collaboration among healthcare stakeholders is critical to work through the challenge of coverage determinations and identify the appropriate patients to ensure those who need the treatment will have access to it.

To date, CSL Behring's discussions with payers and the associated policies that have been written have been positive. As of July 2023, payers who cover 67% of the US population have established clear policies covering HEMGENIX, with over 75% of commercial lives covered.

CSL anticipates that coverage will continue to expand as remaining payers review the clinical and economic evidence for HEMGENIX.

In the spirit of providing formulary decision-makers with the data and resources they need to make informed decisions, the CSL Health Systems team offers payers a customizable access decision model to evaluate the durability and cost impact of HEMGENIX compared with factor IX prophylaxis for their specific plans.

"Giving payers a tool to model durability and the cost impact for their specific plans is crucial because those are the two main considerations," explained James T. Kenney, RPh, MBA, a managed care pharmacy consultant and former manager of specialty and pharmacy contracts at Harvard Pilgrim Health Care, who has studied member retention patterns in adult rare disease cohorts.[33]

"The other question that comes with the value of innovative gene therapies like HEMGENIX is how long patients stay with their health plans, as the investment in these treatments is significant. In my experience, rare disease patients who have plans that are covering them are not likely to leave on their own and studies have proven that to be true."

CSL Behring is providing ongoing training to centers that may administer HEMGENIX and encouraging long-term data collection through the American Thrombosis and Hemostasis Network registry. Registry data will be informative to all stakeholders and will generate additional evidence on the long-term safety, efficacy, and durability of gene therapy.

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A SOLUTION-MINDED **FOCUS**

When innovative treatments like gene therapy come to market, the work doesn't end there

Healthcare providers have to learn and adopt new treatment protocols. Formulary decision-makers must evaluate the value of the treatment while being mindful of economic considerations and patient access goals. Policymakers must ensure healthcare regulations and guidelines support optimal outcomes and protect the well-being of patients.

In today's world, stakeholders need to have the difficult conversations about value, taking into consideration both the short- and long-term clinical benefits, as well as the cost impact to the system at large. If manufacturers are unable to demonstrate value at a given price point, and stakeholders are unable to perceive the value, then the innovation and clinical gains delivered by a new product will not be fully realized. That's not an outcome worthy of such powerful research.

The success of innovative treatments rests as much on solution-minded plan stakeholders collaborating to work through change and new challenges that come with progress, as it does with the research and development teams that bring these game-changing treatments to life.

START A VALUE CONVERSATION

Schedule a meeting with a CSL Account Manager to model durability and cost impact with HEMGENIX at MarketAccess.CSLBehring.com

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IMPORTANT SAFETY INFORMATION

Warning and Precautions

Infusion Reactions

Infusion reactions, including hypersensitivity reactions and anaphylaxis, may occur. Monitor during administration and for at least 3 hours after end of infusion. If symptoms occur, slow or interrupt administration. Re-start administration at a slower infusion once resolved.

Hepatotoxicity/Hepatocellular Carcinoma

Post-dose, monitor for elevated transaminase levels. Consider corticosteroid treatment should elevations occur. The integration of liver-targeting AAV vector DNA into the genome may carry the theoretical risk of hepatocellular carcinoma development. For patients with preexisting risk factors for hepatocellular carcinogenicity, perform regular (eg, annual) abdominal ultrasound and alpha-fetoprotein testing following administration.

Immune-mediated neutralization of the AAV5 vector capsid

Preexisting neutralizing anti-AAV antibodies may impede transgene expression at desired levels.

Monitoring Laboratory Tests

In addition to monitoring liver function, monitor for Factor IX activity and Factor IX inhibitors after administration.

Adverse Reactions

The most common adverse reactions (incidence ≥5%) were elevated ALT, headache, blood creatine kinase elevations, flu-like symptoms, infusion-related reactions, fatigue, nausea, malaise, and elevated AST.

Indication

HEMGENIX® (etranacogene dezaparvovec-drlb) is an adeno-associated virus vector-based gene therapy indicated for the treatment of adults with Hemophilia B (congenital Factor IX deficiency) who:

- Currently use Factor IX prophylaxis therapy, or
- Have current or historical life-threatening hemorrhage, or
- Have repeated, serious spontaneous bleeding episodes.

HEMGENIX is for single use intravenous infusion only.

Contraindications: None.

Please see full Prescribing Information for HEMGENIX at **www.hemgenix.com/hcp**.

To report SUSPECTED ADVERSE REACTIONS, contact the CSL Behring Pharmacovigilance Department at 1-866-915-6958 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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