

BMN 270 – Gene Therapy for Hemophilia A

Gene Therapy for hemophilia is a treatment approach under investigation in clinical trials and is not approved for commercial use by any regulatory authority

Hemophilia A, a Rare Bleeding Disorder

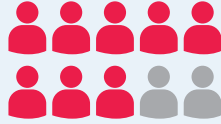
Hemophilia A is a rare bleeding disorder caused by mutation in a single gene that provides instructions to make a protein called Factor VIII, which is essential for blood to clot normally



Patients with moderate-to-severe hemophilia are at risk for **spontaneous bleeding, as well as excessive bleeding from minor cuts, falls or even activities** of daily life that would not affect people without hemophilia



Hemophilia A:

- Occurs as the most common form of two major inherited hemophilia subtypes
- Accounts for **eight out of 10 cases** of hemophilia¹

- Affects approximately **1 in 5K** to **1 in 10K** births^{2,3}
- Impacts mostly males, as mutations are passed on as a **recessive X chromosomal** manner. Females can also be affected.



BMN 270 Clinical Program*



BMN 270 is an investigational gene therapy treatment for hemophilia A



BMN 270 is an AAV-Factor VIII with the goal to empower patients' cells to safely produce and restore their own FVIII protein levels, such that patients can clot normally



AAV does not cause disease in humans



The **Phase 1/2 clinical trial** is a dose escalation study with the goal of monitoring safety and changes in Factor VIII levels



The study will continue to monitor the **15 patients** who have received this investigational therapy for this study

The primary endpoints of the study are to assess:

- Safety
- Determine the proper dose

The study is evaluating:

- Impact of BMN 270 on the frequency of Factor VIII replacement therapy
- Number of bleeding episodes requiring treatment
- Immune responses to gene therapy

Innovation in Hemophilia

We are focused on new technologies for people living with hemophilia A through the development of our investigational gene therapy. We've brought together leading scientific and clinical experts to pioneer the way. Our development team includes Dr. Barrie Carter, the scientist who first introduced using the adeno-associated virus as a gene therapy delivery vehicle; Dr. Gordon Vehar, who led the scientific team that first cloned Factor VIII; and Dr. Wing Yen Wong, a hematologist with decades of experience in the clinical arena and in developing novel therapies for hemophilia patients.

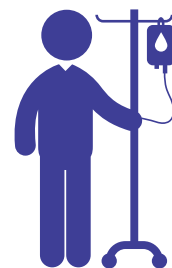


Gene Therapy for Hemophilia A



Gene therapy is a treatment approach under investigation for hemophilia A patients, designed to correct the underlying genetic defect of the disease.

The goal of gene therapy is to provide patients with the genetic code that will enable their bodies to manufacture and maintain a constant level of Factor VIII. This would have the potential to reduce bleeds or eliminate abnormal bleeding into joints and other organs, and possibly eliminating the requirement for multiple lifelong exogenous factor replacement therapy.



How It Works:

- 1) The functional gene is inserted into a vector or vehicle containing the DNA sequence coding for Factor VIII.
- 2) The objective is for the cells to then use the information to build the functional protein that the body needs, potentially reducing or eliminating the cause of the disease.



***Potential Risks:** It is important to understand that this is an experimental therapy in an early stage of clinical development. In hemophilic Factor VIII deficient mouse models of hemophilia A, BMN 270 restored Factor VIII plasma concentrations to levels projected to be adequate for normal clotting in humans. In the Phase I/II clinical study, no patients developed inhibitors to Factor VIII and no patients withdrew from the study. The most common adverse events (AEs) across all dose cohorts were mild alanine aminotransferase (ALT) elevations (10 patients), arthralgia (7 patients) and back pain, fatigue, headache (5 patients each). Two patients reported Serious Adverse Events (SAEs) during the study. One patient was hospitalized for observation after developing Grade 2 pyrexia with myalgia and headache within 24 hours of receiving BMN 270. The event resolved within 48 hours following treatment with paracetamol without further intervention. The event was assessed as related to BMN 270. Another patient underwent an elective total knee replacement to treat hemophilic arthropathy. No surgical complications were reported. This Grade 1 SAE was assessed to be unrelated to BMN 270. AEs of ALT elevation were reported in 11 of the 15 patients. All events of ALT elevation were mild (Grade 1) and non-serious.⁴ Safety of the investigational compound is still under evaluation.

1. "Hemophilia A." National Hemophilia Foundation. Last accessed on July 14, 2016. Available here: www.hemophilia.org/Bleeding-Disorders/Types-of-Bleeding-Disorders/Hemophilia-A.
2. "What Is Hemophilia?" National Heart, Lung and Blood Institute. Last accessed on July 14, 2016. Available here: www.nhlbi.nih.gov/health/health-topics/topics/hemophilia.
3. "About Bleeding Disorders: Frequently Asked Questions." World Federation of Hemophilia. Last accessed on July 14, 2016. Available here: www.wfh.org/en/page.aspx?pid=637#How_common.
4. "Clinical Update from International Society on Thrombosis and Haemostasis (ISTH) 2017 Congress on 7/11/17"

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INVESTIGATIONAL
GENE THERAPY BY
B:OMARIN®

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At BioMarin, we develop first-in-class and best-in-class treatments that provide meaningful advancements for people with serious and life-threatening rare genetic diseases. Our 20-year track record of bringing innovative technologies to disease areas has enabled strong, long-standing relationships with the communities we serve.

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1. Gene Therapy Study in Severe Haemophilia A Patients. Clinicaltrials.gov. BioMarin. Last accessed on June 28, 2017. Available here: <https://clinicaltrials.gov/ct2/show/NCT02576795?term=BMN+270&rank=1>

2. "Clinical Update from International Society on Thrombosis and Haemostasis (ISTH) 2017 Congress on 7/11/17"