Valoctocogene Roxaparvovec –
Gene Therapy for Hemophilia A Undergoing Clinical Trials

Gene therapy for hemophilia is a treatment approach undergoing clinical studies and is not approved for commercial use by any regulatory authority

BIOMARIN®

Gene Therapy for Hemophilia A Undergoing Clinical Trials[1,2]

1 The DNA sequence for the functional **factor VIII gene** is inserted into a gene depleted viral vector

2 The modified **DNA sequence is packaged into a viral vector,** in this case the non-pathogenic adeno-associated virus (AAV) vector

3 The vector is given to the person with hemophilia via **a single IV infusion**

4 Once infused, the vector is **transports the functional DNA to the liver cells**

5 The functional **factor VIII gene** is deposited into the cell's nucleus and the capsid degrades

6 Cells with the revised gene may be able to make the correct **factor VIII protein,** which is necessary for blood to clot normally

7 Corrected genes are **only present in the cells** transduced with the vector. Current evidence supports that the delivered genetic material is neither passed down to future generations or to those in contact with the gene therapy recipient

Valoctocogene Roxaparvovec Clinical Trial Program*

Valoctocogene roxaparvovec is an AAV-based** gene therapy treatment for hemophilia A undergoing clinical trials. The safety and efficacy of the treatment has not been established.

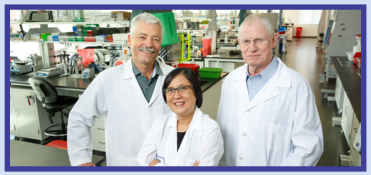
The Most Advanced Hemophilia A Gene Therapy Clinical Trial Research Program:

First and only to report two-year safety and efficacy data

First to initiate a Phase 3 trial (December 2017), which will enroll 130 participants.

Most clinical trials (six) underway, eligibility requires participants to have less than 1 percent Factor VIII activity level:

- **a.** Two global Phase 3 trials: GENEr8-1 (6e13 vg/kg*dose) and GENEr8-2(4e13 vg/kg* dose)
- **b.** Phase 1/2 dose escalation study
- **c.** Phase 1/2 trial in participants with pre-existing adeno-associated vector (AAV5) antibodies
- **d.** Two non-interventional studies: AAV5 seroprevalence and baseline characteristics in participants with hemophilia A



Innovation in Hemophilia

We are focusing on researching new technologies for people living with hemophilia A through the development of our gene therapy, valoctocogene roxaparvovec, undergoing clinical trials. We have brought together the pioneering scientific and clinical experts to lead the way. Our development team includes Dr. Barrie Carter, the scientist who first described the successful use of AAV for gene transfer into cells (1984)[9]. Dr. Gordon Vehar, who led the scientific team that first cloned factor VIII (1984)[10]; and Dr. Wing Yen Wong, a hematologist with decades of experience in the clinical arena and in developing novel therapies for people with hemophilia

Hemophilia A, a Rare Bleeding Disorder

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

People with moderate-to-severe hemophilia are at risk for spontaneous bleeding, as well as excessive bleeding from minor cuts, falls or even normal 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 hemophilia[3]
- Affects approximately **1 in 5K** to **1 in 10K** births[4,5]
- Impacts mostly males, as mutations are passed on in a **recessive X chromosomal** manner. Females can also be affected

Gene Therapy Manufacturing

BIOMARIN HAS CONSTRUCTED ONE OF THE FIRST GENE THERAPY MANUFACTURING FACILITIES OF ITS KIND

Since it's completion in 2017, everything from production to putting product into vials is done at the facility

MEETING CLINICAL & COMMERCIAL DEMAND

Ability to produce

4,000 DOSES / YEAR

OF VALOCTOCOGENE ROXAPARVOVEC

OWNED MANUFACTURING APPROACH ALLOWS:

- CONTROL OF SCHEDULING
- QUALITY
- RAPID PRODUCTION

***Potential Risks:**[8] The most common adverse events (AEs) across all dose cohorts in 2 years of follow-up data were alanine aminotransferase (ALT) elevation (11 people with hemophilia, 73%); arthralgia, aspartate aminotransferase elevation, and headache (7 people each, 47%); back pain and fatigue (5 people each, 33%). Two people reported Serious Adverse Events (SAEs) during the study. One person was hospitalized for observation after developing Grade 2 pyrexia with myalgia and headache within 24 hours of receiving valoctocogene roxaparvovec. The event resolved within 48 hours following treatment with paracetamol, an over-the-counter treatment for pain and fever. The event was assessed as related to valoctocogene roxaparvovec. The other SAE was assessed as not related to valoctocogene roxaparvovec, attributed to a planned knee surgery to treat hemophilic arthropathy, and Grade 1 in severity. No complications were reported.

*4e13 vg/kg and 6e13 vg/kg refer to doses of 4 and 6 x10^13 vector genomes per kilogram body weight, respectively
**adeno-associated virus

1. NIH. How does gene therapy work? http://ghr.nlm.nih.gov/primer/therapy/procedures Accessed October 9, 2017
2. Naso MF, Tomkowicz B, Perry WL and Strohl WR. Adeno-Associated Virus (AAV) as a Vector for Gene Therapy. BioDrugs. 2017; 31(4):317-334
3. "Hemophilia A." National Hemophilia Foundation. Last accessed on July 14, 2016. Available here: www.hemophilia.org/Bleeding-Disorders/Types-of-Bleeding-Disorders/Hemophilia-A.
4. "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.
5. "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.
6. https://clinicaltrials.gov/show/NCT03392974
7. https://clinicaltrials.gov/show/NCT03370913
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9. Carter, B. Adeno-associated virus and the development of adeno-associated virus vectors: a historical perspective. Molecular Therapy. Volume 10, Issue 6. Dec. 2004. Pages 981-989.
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