November 2019

BioMarin Hemophilia A Clinical Development Program: An Update for the Hemophilia Community

BioMarin is pleased to update the community regarding our gene therapy clinical trial program in Hemophilia A.

Clinical Trial Update
BioMarin’s investigational gene therapy valoctocogene roxaparvovec, is currently being studied in adults with severe Hemophilia A.

The first Phase 1/2 study was initiated in 2015 and consists of 15 individuals in long-term follow-up, post treatment with valoctocogene roxaparvovec.

The Phase 3 study is currently being conducted in 13 countries and 130 patients have been enrolled and have received investigational gene therapy.

Regulatory Status
The EMA recently granted BioMarin's accelerated assessment of valoctocogene roxaparvovec, for adults with severe Hemophilia A. Additionally, the FDA has granted valoctocogene roxaparvovec Breakthrough Therapy designation. Valoctocogene roxaparvovec has Orphan Drug designation from the Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

BioMarin plans to submit marketing applications in United States and Europe before the end of 2019 which will allow regulators to evaluate the safety and efficacy of valoctocogene roxaparvovec.

BioMarin's investigational gene therapy for Hemophilia A has not been approved for use; it is in ongoing clinical trials evaluating its safety and efficacy.

A patient's medical team remains the best source of information regarding any health effects of hemophilia.

For inquiries from Patient Advocacy Organizations please contact patientadvocacy@bmrn.com. For further information on BioMarin Hemophilia A studies please visit www.clinicaltrials.gov or contact BioMarin Medical Information at medinfo@bmrn.com.
BioMarin is pleased to update the community regarding our gene therapy clinical trial program in hemophilia A. BioMarin's investigational gene therapy for hemophilia A has not been approved for use; it is in ongoing clinical trials evaluating its safety and efficacy.

**Ongoing Clinical Studies**

BioMarin’s valoctocogene roxaparvovec, previously known as BMN 270, is currently being investigated in adults with severe hemophilia A. There are six studies that are part of the program.

- The first Phase 1/2 study was initiated in 2015 and consists of 15 individuals in long-term follow-up, post treatment with valoctocogene roxaparvovec.
- A global seroprevalence study seeks to determine the frequency of individuals who have a pre-existing antibody against different serotypes of adeno-associated virus (AAV).
- A non-interventional study seeks to evaluate the rates of bleeding episodes and FVIII use, as well as health-related quality of life, in participants receiving FVIII prophylaxis.
- The Phase 3 program consists of two global studies (named GENEr8-1 and GENEr8-2) to evaluate two dose levels, 6E13 and 4E13 vg/kg, respectively of valoctocogene roxaparvovec.
  - The GENEr8-1 study is currently being investigated in 12 countries to include 130 participants and is expected to be fully enrolled in the third quarter of 2019.
- In addition, a Phase 1/2 study evaluating the safety of valoctocogene roxaparvovec in participants who have a pre-existing antibody against AAV serotype 5, the vector used in valoctocogene roxaparvovec, is open for enrollment at a limited number of sites in the UK.

On May 28, 2019, BioMarin released an update on the Phase 1/2 study of valoctocogene roxaparvovec, including the most recent results based on 3 years of follow-up data for individuals who received the 6E13 vg/kg dose. Additionally our BioMarin medical team will inform Principal Investigators and Key Opinion Leaders within the community, including those that represent your organization, about this development.

**Regulatory Status**

The U.S. Food and Drug Administration (FDA) has granted valoctocogene roxaparvovec Breakthrough Therapy Designation, and it has also been given access to the Priority Medicines (PRIME) regulatory initiative from the European Medicines Agency (EMA). Valoctocogene roxaparvovec has previously received orphan drug designation from the FDA and European Commission. This designation is intended to facilitate and expedite development and review of new therapies for patients with serious conditions for which there is still unmet need, allowing them to benefit as early as possible.
For general inquiries from advocacy organizations, please contact patientadvocacy@bmrn.com. For further information on BioMarin clinical studies, please visit www.clinicaltrials.gov or contact BioMarin Medical Information at medinfo@bmrn.com or by phone: Toll Free 1-800-983-4587; Local (651) 523-0310. Your medical team remains the best source of information for you about any health effects of hemophilia A.
BioMarin BMN 270 Hemophilia A Program Update

On September 6, 2018, BioMarin presented an update to our investigational therapy program for Hemophilia A at the Citi Biotech Conference. Being transparent and communicating updates on our clinical program with the Advocacy community is very important to us. Equally as important is fielding any questions you may have on these announcements. For this reason, our BioMarin medical team has informed all of our Principal Investigators and Key Opinion Leaders within the community, including NHF, HFA and WFH (Dr Pipe and Glenn Pierce); EHC (Flora Peyvandi). Should you have any scientific questions, please feel free to reach out to them or, should you wish to schedule a call with BioMarin medical personnel, we can arrange that as well.

Key Program updates:

BMRN Positioning for Accelerated Approval
BioMarin plans to file for accelerated approval for its investigational gene therapy for hemophilia, valoctocogene roxaparvovec, in H2 2019 (~1 year ahead of our previous H2 2020 expectation). The company arrived at this decision based on careful evaluation of the recent hemophilia gene therapy FDA guidance.

Valrox Protocol Updates
BioMarin expects to dose all patients in GENEr8-1 (dose 6E13 vg/kg) by Q2 2019, an adjustment from previously disclosed Q1 2019. The increase in enrollment numbers to 130 from 70 and the global nature of the clinical trials are the reasons for this adjustment. In addition, BioMarin is slightly restricting the enrollment criteria for the GENEr8 studies, to match the enrollment criteria from the Phase 2. Moving forward, the trial will not include patients that have HIV or mild liver disease. This change was the result of two patients having higher liver function test (LFT) elevations than what were seen in the Phase 2. The Valrox registration program continues to manage LFT elevations on demand and there is no inclusion or addition of steroid prophylaxis to the protocol as a result. Ultimately, these LFT elevations aren’t unexpected given data across other gene therapy studies and we highlight that both patients are asymptomatic and the LFT elevations are resolving.

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In closing, we would like to remind you of our commitment to transparency. Should you have any questions, please do not hesitate to reach out to us and we would be happy to field them.
BioMarin is continuing clinical development of an investigational gene therapy for the treatment of hemophilia A, known as valoctocogene roxaparvovec. The therapy is designed to use a carrier (known as a “vector”) to deliver a functional Factor VIII (FVIII) gene to a patient’s cells. Research is ongoing to determine whether once inside cells, the body can use this new DNA to produce normal functioning FVIII protein. The safety and efficacy of valoctocogene roxaparvovec has not been established.

Phase 1/2 Study update (BMN 270-201)

On May 22, 2018, BioMarin presented an update on the Phase 1/2 study of valoctocogene roxaparvovec. The most recent results based on 2 years of data were presented at the World Federation of Hemophilia (WFH) Meeting by John Pasi M.B., Ch.B., Ph.D from Barts and the London School of Medicine and Dentistry, who is the primary investigator for this Phase 1/2 study.

Phase 3 Studies (GENEr8-1 and GENEr8-2)

In December of 2017, we opened two global Phase 3 studies for valoctocogene roxaparvovec. GENEr8-1 will evaluate a 6e13 vg/kg dose and GENEr8-2 will evaluate a 4e13 vg/kg dose. Both Phase 3 GENEr8 studies will assess the efficacy and safety of valoctocogene roxaparvovec in men over 18 with severe hemophilia A.

Both GENEr8-1 and GENEr8-2 have enrolled patients and are actively recruiting. For further information on our Phase 3 studies, please visit www.clinicaltrials.gov, GENEr8-1 study number: NCT03370913 and GENEr8-2 study number: NCT03392974.

Gene Therapy Manufacturing Facility Recognized with Industry Award

We have previously shared that BioMarin constructed the largest gene therapy manufacturing facility in the world, which is located in Novato, California. We are proud to announce that on Tuesday, March 20th, during the 2018 Europe Annual Conference in Rome, Italy, the International Society for Pharmaceutical Engineering (ISPE) selected the company’s gene therapy manufacturing facility as the 2018 Facility of the Year Category Winner for Project Execution. With the company’s hemophilia A investigational treatment valoctocogene roxaparvovec in global Phase 3 development and a need to produce material for the clinical studies and potentially for commercial demand, BioMarin converted an office building into an 18,000 square foot gene therapy facility in less than a year. As a result of this new gene therapy manufacturing capability, the company is well positioned with the necessary resources and capacity to continue with the development program for valoctocogene roxaparvovec in severe hemophilia A.

Regulatory Status

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