BioMarin's BMN 331 Hereditary Angioedema (HAE) Investigational Gene Therapy Program: An Update for the HAE Community.

BioMarin is preparing for the first patient to be dosed in early 2022 into its Phase I/II gene therapy trial (HAERMONY-1), researching the safety and efficacy of BMN 331.

What is BMN 331?

BMN 331, is the name given to the investigational gene therapy BioMarin is researching. It has not been approved for use outside of a clinical trial and has not been determined to be safe or effective.

HAE is a rare genetic disorder characterized by unpredictable, painful, recurring, and self-limiting acute edematous attacks which may occur at multiple locations such as the face, extremities, upper airways, and the gastrointestinal tract. The main type of HAE is caused by mutations in the SERPING1 gene. This gene encodes a protein called C1-INH* which plays an important role in controlling certain types of swelling in the body. When C1-INH is missing or not working correctly, sudden, unexpected swelling events can occur.

BMN 331 will be researched to understand the safety of administration of the investigational gene therapy and to measure any impact on the ability of individuals to produce their own functional C1-INH protein.

Please note that BMN 331 is an investigational gene therapy; the safety and efficacy in humans has not yet been determined.

About BioMarin

BioMarin is a global pharmaceutical company with 7 approved therapies and more than 20 years of experience in developing innovative medicines for rare genetic conditions. Each investigative medicine we pursue is guided by a fundamental understanding of the genetics and underlying biology of the condition it will address. We are committed to providing a big impact with a focus on rare disorders.

For additional information:

- For inquiries or to provide feedback from advocacy organizations, please contact patientadvocacy@bmrn.com
- Contact BioMarin Medical Information at medinfo@bmrn.com

*C1 esterase inhibitor (C1-INH) is a protein found in the fluid part of the blood. It controls a protein called C1, which is part of the complement system.

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On 14 November 2019, BioMarin introduced its third investigational gene therapy candidate, BMN 331, for the treatment of HAE.

Clinical trials in patients with HAE have been authorized to begin based on authorization from the Food and Drug Administration (FDA) following submission of an Investigational New Drug Application (IND). The FDA assesses the safety of the intended research study as documented by the IND application to assure that human clinical trial participants will not be subjected to an unreasonable risk. This approval gives BioMarin authorization to begin clinical trials with BMN 331 in the last quarter of 2021. BioMarin is actively preparing clinical trial regulatory submissions for other countries worldwide.

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BMN 331 will be researched to see if it can introduce the SERPING1 gene into the body, the safety profile, and whether it can enable individuals to produce their own functional C1-INH protein.

Please note that BMN 331 is currently under investigation; the safety and efficacy in humans has not yet been determined.

***C1 esterase inhibitor (C1-INH) is a protein found in the fluid part of the blood. It controls a protein called C1, which is part of the complement system.**

What is the Clinical Trial process?

The stages of clinical trials are represented as phases of clinical development. Clinical trials are normally conducted in four phases however, for rare diseases, Phase 1 and Phase 2 of clinical trials are often combined to a phase known as Phase 1/2. The aim of Phase 1 clinical trials is to find out the safe dose range and to look for any side effects. The aim of Phase 2 clinical trials is to find out if the treatment has any beneficial effects on the disease. Phase 1/2 clinical trials for rare diseases generally involve a small number of patients than clinical trials for more common diseases.

Phase 1: A study drug is tested in people, often in volunteers without disease, for the first time to evaluate its safety and best practices for administering the drug.

Phase 2: The study drug is tested to determine a safe dose or range of doses, to further evaluate its safety, and to begin testing in subjects with the disease of interest to determine if it has the intended or predicted effects.

Phase 3: The study drug is tested, often in larger trials of longer duration, to measure its effectiveness and to further evaluate safety. Phase 3 trials often compare the study drug to commonly used treatments (if any) or to placebo treatment, if it is scientifically and ethically appropriate to do so.

Phase 4: Post-marketing studies are performed after regulatory agency approval occurs. These studies are designed to collect additional information including the drug's risks, benefits and optimal use in a broader patient population often over extended periods of time. An example of a Phase 4 study would be the registry to collect medical information on the disease population, whether they are taking the approved drug or not.

Regulatory Review

When Phase 1–3 clinical trials are completed, a Marketing Application (e.g., a New Drug Application (NDA) for the US FDA, or a Marketing Authorization Application (MAA) for the European Authorities) is submitted to regulatory agencies. The Marketing Application contains all data gathered about the safety and effectiveness of the study drug from the preclinical studies and clinical trials that have been performed. The Marketing Application also contains information about the chemistry, toxicology, pharmacology and manufacturing processes of the product. The regulatory agency reviews the data and, if approved, the new treatment can be marketed and distributed to the public through prescription by a qualified physician.

Who is BioMarin?

BioMarin is a biotechnology company, headquartered in San Rafael, California with offices and manufacturing facilities located globally. BioMarin specializes in developing therapies for patients with rare diseases.

Your medical team remains the best source of advice for you or your family regarding HAE.

For additional information:

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- Contact BioMarin Medical Information at medinfo@bmrn.com

Hereditary Angioedema Clinical Development Program

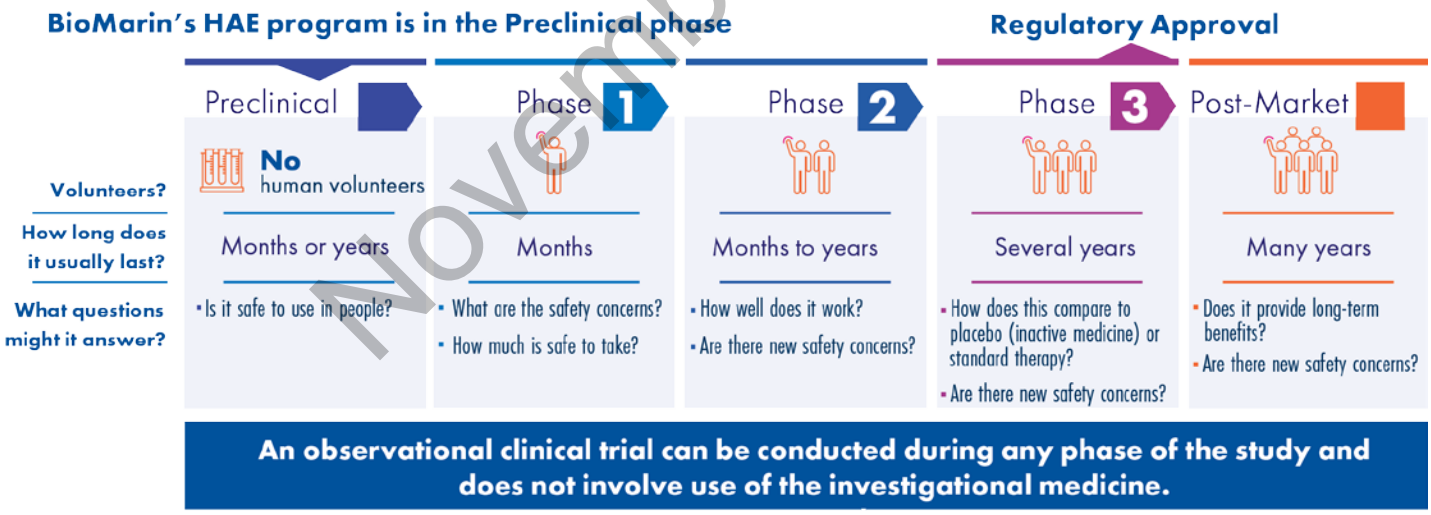
An Update for the Community

BioMarin is a global pharmaceutical company with 6 approved therapies and more than 20 years of experience in developing innovative medicines for rare genetic conditions. BioMarin is invested in following ground-breaking science to bring a big impact to small populations. **Patients are at the heart of what we do.**

In November 2019, BioMarin announced expanding research to include an investigational gene therapy for Hereditary Angioedema (HAE), known as BMN 331.

Before a new treatment can be made available, it must go through careful testing in clinical studies to see if it is safe and effective. BMN 331 has not yet begun clinical studies in humans and has not been proven safe or effective. BioMarin is actively working with regulatory agencies on an investigational new drug (IND) application in order to start clinical studies in 2021.

The bigger picture



About Gene Therapy

Adeno-associated virus (AAV) based gene transfer therapy is one method of gene therapy being investigated. It aims to introduce a functional (or working) gene into the body which is intended to allow the body to produce needed proteins that it lacks. In AAV gene transfer research, a functional gene is inserted into a neutralized viral shell (or therapeutic vector) which delivers the new gene into the target tissue via a single IV infusion. After administration, clinical trial participants are closely monitored to collect data regarding the impact of the infusion on safety and efficacy. There is no replacement or editing done at a genetic level—gene therapy research seeks to introduce a new gene into the body which is not intended to be passed down to future generations.

Hereditary Angioedema Clinical Development Program

An Update for the Community

About BMN 331

The main types of HAE are caused by a mutation (or change) in the SERPING1 gene. This gene is responsible for making a protein called C1-INH (C1-inhibitor) which plays an important role in controlling certain types of swelling in the body. When C1-INH is missing or not working correctly, sudden, unexpected swelling events can occur. BMN 331 is being researched to see if it can introduce a SERPING1 gene into the liver, to evaluate the safety risks as well as whether it can produce the desired protein. BMN331 has not been approved for use and has not been determined to be safe or effective.

Gene Therapy Manufacturing

BioMarin has built one of the first gene therapy manufacturing facilities of its kind in the world. This facility can support a number of disease areas. The BMN 331 research program will leverage development and manufacturing experience from BioMarin's ongoing gene therapy research in hemophilia A and phenylketonuria.

For additional information on the BioMarin HAE program:

- Contact BioMarin Medical Information at 1-800-983-4587 or medinfo@bmrn.com
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