

## **First Gene Therapy for Adults with Severe Hemophilia A, BioMarin's ROCTAVIAN™ (valoctocogene roxaparvovec), Approved by European Commission (EC)**

*Maintains Orphan Drug Designation (ODD) in the EU Providing 10-years of Market Exclusivity*

*Significant Benefit Over Existing Therapies for Patients with Severe Hemophilia A in EU Based on EMA Determination of ODD*

*Conference Call and Webcast to be Held Wed., Aug. 24th at 8:00 pm Eastern*

SAN RAFAEL, Calif., Aug. 24, 2022 /[PRNewswire](#)/ -- BioMarin Pharmaceutical Inc. (NASDAQ: BMRN) today announced that the European Commission (EC) has granted conditional marketing authorization (CMA) to ROCTAVIAN™ (valoctocogene roxaparvovec) gene therapy for the treatment of severe hemophilia A (congenital Factor VIII deficiency) in adult patients without a history of Factor VIII inhibitors and without detectable antibodies to adeno-associated virus serotype 5 (AAV5). The EC also endorsed EMA's recommendation for Roctavian to maintain orphan drug designation, thereby granting a 10-year period of market exclusivity. The EMA recommendation noted that, even in light of existing treatments, Roctavian may potentially offer a significant benefit to those affected with severe Hemophilia A. The one-time infusion is the first approved gene therapy for hemophilia A and works by delivering a functional gene that is designed to enable the body to produce Factor VIII on its own without the need for continued hemophilia prophylaxis, thus relieving patients of their treatment burden relative to currently available therapies. People with hemophilia A have a mutation in the gene responsible for producing Factor VIII, a protein necessary for blood clotting.

It is estimated that more than 20,000 adults are affected by severe hemophilia A across more than 70 countries in Europe, the Middle East, and Africa. Of the 8,000 adults with severe hemophilia A in the 24 countries within BioMarin's footprint covered by today's EMA approval, there are an estimated 3,200 patients who will be indicated for Roctavian. BioMarin anticipates additional access to ROCTAVIAN™ for patients outside of the EU through named patient sales based on the European Medicines Agency (EMA) approval in countries in the Middle East, Africa and Latin America and expects additional market registrations to be facilitated by the EMA license.

"This approval in the EU represents a medical breakthrough in the treatment of patients with severe hemophilia A that expands the conversation between a patient and physician on treatment choices to now include a one-time infusion that protects from bleeds for several years," said Professor Johannes Oldenburg, Director of the Institute of Experimental Haematology and Transfusion Medicine and the Haemophilia Centre at the University Clinic in Bonn, Germany. "It is exciting to imagine the possibilities of this approved gene therapy, which has demonstrated a substantial and sustained reduction in bleeding for patients, who potentially could be freed from the burden of regular infusions."

"Roctavian approval in Europe is a historic milestone in medicine and is built upon almost four decades of scientific discovery, innovation, and perseverance. We thank the European Commission for recognizing Roctavian's value as the first gene therapy for hemophilia A, a feat that we believe will transform how healthcare professionals and the patient community think about caring for bleeding disorders," said Jean-Jacques Bienaimé, Chairman and Chief Executive Officer of BioMarin. "We are grateful to the patients, investigators and community, who dedicated their time and effort to this achievement and whose aspirations provided the driving force behind making this one-time therapy a reality."

The EC based its decision on a significant body of data from the Roctavian clinical development program, the most extensively studied gene therapy for hemophilia A, including two-year outcomes from the global GENER8-1 Phase 3 study. The GENER8-1 Phase 3 study demonstrated stable and durable bleed control, including a reduction in the mean annualized bleeding rate (ABR) and the mean annualized Factor VIII infusion rate. In addition, the data included five and four years of follow-up from the 6e13 vg/kg and 4e13 vg/kg dose cohorts, respectively, in the ongoing Phase 1/2 dose escalation study. BioMarin has committed to continue working with the broader community and the EMA to monitor the long-term effects of treatment. The Product Information will be available shortly on the EMA website under the [Medicines tab](#). Search for "ROCTAVIAN" and select "Human medicine European public assessment report (EPAR): Roctavian. Then select "Product Information" in the Table of Contents and then select "Roctavian: EPAR – Product Information."

A Conditional Marketing Authorization (CMA) recognizes that the medicine fulfils an unmet medical need based on a positive benefit-risk assessment, and that the benefit to public health of the immediate availability on the market outweighs the uncertainties inherent to the fact that additional data are still required. BioMarin will provide further data from ongoing studies within defined timelines to confirm that the benefits continue

to outweigh the risks, building on what already constitutes the largest clinical data package for gene therapy in hemophilia A. Conversion to a standard marketing authorization will be contingent on the provision of additional data from currently ongoing Roctavian clinical studies, including longer-term follow up of patients enrolled in the pivotal trial GENE8-1, as well as a study investigating efficacy and safety of ROCTAVIAN with prophylactic use of corticosteroids (Study 270-303), for which enrollment is now complete.

Orphan drug designation is reserved for medicines treating rare (affecting not more than five in 10,000 people in the EU), life-threatening or chronically debilitating diseases. Authorized orphan medicines benefit from ten years of market exclusivity, protecting them from competition with similar medicines with the same therapeutic indication, which cannot be marketed during the exclusivity period.

BioMarin remains committed to bringing Roctavian to eligible patients with severe hemophilia A in the United States and is targeting a Biologics License Application (BLA) resubmission for Roctavian by the end of September 2022. Typically, BLA resubmissions are followed by a six-month review procedure. However, the Company anticipates three additional months of review may be necessary based on the number of data read-outs that will emerge during the procedure.

### **Robust Clinical Program**

BioMarin has multiple clinical studies underway in its comprehensive gene therapy program for the treatment of hemophilia A. In addition to the global Phase 3 study GENE8-1 and the ongoing Phase 1/2 dose escalation study, the Company is also conducting a Phase 3B, single arm, open-label study to evaluate the efficacy and safety of Roctavian at a dose of  $6 \times 10^{13}$  vg/kg with prophylactic corticosteroids in people with hemophilia A (Study 270-303). Also ongoing are a Phase 1/2 Study with the  $6 \times 10^{13}$  vg/kg dose of Roctavian in people with hemophilia A with pre-existing AAV5 antibodies (Study 270-203) and a Phase 1/2 Study with the  $6 \times 10^{13}$  vg/kg dose of Roctavian in people with hemophilia A with active or prior Factor VIII inhibitors (Study 270-205).

### **Safety Summary**

Overall, single  $6 \times 10^{13}$  vg/kg dose of Roctavian has been well tolerated with no delayed-onset treatment related adverse events. The most common adverse events (AE) associated with Roctavian occurred early and included transient infusion associated reactions and mild to moderate rise in liver enzymes with no long-lasting clinical

sequelae. Alanine aminotransferase (ALT) elevation (113 participants, 80%), a laboratory test of liver function, remained the most common adverse drug reaction. Other adverse reactions included aspartate aminotransferase (AST) elevation (95 participants, 67%), nausea (52 participants, 37%), headache (50 participants, 35%), and fatigue (42 participants, 30%). No participants developed inhibitors to Factor VIII, thromboembolic events or malignancy associated with Roctavian.

## **About Hemophilia A**

People living with hemophilia A lack sufficient functioning Factor VIII protein to help their blood clot and are at risk for painful and/or potentially life-threatening bleeds from even modest injuries. Additionally, people with the most severe form of hemophilia A (Factor VIII levels <1%) often experience painful, spontaneous bleeds into their muscles or joints. Individuals with the most severe form of hemophilia A make up approximately 50 percent of the hemophilia A population. People with hemophilia A with moderate (Factor VIII 1-5%) or mild (Factor VIII 5-40%) disease show a much-reduced propensity to bleed.

Individuals with severe hemophilia A are treated with a prophylactic regimen of intravenous Factor VIII infusions administered 2-3 times per week (100-150 infusions per year) or a bispecific monoclonal antibody that mimics the activity of Factor VIII administered 1-4 times per month (12-48 infusions per year). Despite these regimens, many people continue to experience breakthrough bleeds, resulting in progressive and debilitating joint damage, which can have a major impact on their quality of life.

Hemophilia A, also called Factor VIII deficiency or classic hemophilia, is an X-linked genetic disorder caused by missing or defective Factor VIII, a clotting protein. Although it is passed down from parents to children, about 1/3 of cases are caused by a spontaneous mutation, a new mutation that was not inherited. Approximately 1 in 10,000 people have hemophilia A.

## **Conference Call and Webcast to be Held Wed., Aug. 24<sup>th</sup> at 8:00 pm Eastern**

BioMarin will host a conference call and webcast to discuss the EC approval today, Wed., Aug. 24<sup>th</sup> at 8:00 pm Eastern. This event can be accessed in the investor section of the BioMarin website at <https://investors.biomin.com/events-presentations>.

U.S./Canada Dial-in Number: 800-831-4163	Replay Dial-in Number: 800-645-7964
International Dial-in Number: 213-992-4616	Replay International Dial-in Number: 757-849-6722

(No ID required for live call)	Playback ID: 9184
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## **About BioMarin**

BioMarin is a global biotechnology company that develops and commercializes innovative therapies for people with serious and life-threatening genetic diseases and medical conditions. The Company selects product candidates for diseases and conditions that represent a significant unmet medical need, have well-understood biology and provide an opportunity to be first-to-market or offer a significant benefit over existing products. The Company's portfolio consists of eight commercial products and multiple clinical and preclinical product candidates for the treatment of various diseases. For additional information, please visit [www.biomarin.com](http://www.biomarin.com).

## **Forward-Looking Statements**

This press release contains forward-looking statements about the business prospects of BioMarin Pharmaceutical Inc. (BioMarin), including without limitation, statements about: the number of adults across Europe, the Middle East, and Africa who are affected by severe hemophilia A; the number of adults in the countries within BioMarin's footprint covered by the EMA approval who have severe hemophilia A and are indicated for Roctavian; BioMarin anticipating additional access to Roctavian for patients outside of the EU through named patient sales based on the EMA approval in countries in the Middle East, Africa and Latin America and the expectation that additional market registrations will be facilitated by the EMA license; the potential for Roctavian to be a one-time infusion protecting patients from bleeds for several years and freeing them from the burden of regular infusions; Roctavian potentially offering a significant benefit to those affected with severe hemophilia A; Roctavian potentially transforming how healthcare professionals and the patient community think about caring for bleeding disorders; BioMarin's plans to provide further data from ongoing studies within defined timelines to confirm that the benefits of Roctavian continue to outweigh the risks; conversion of Roctavian's CMA to a standard marketing authorization; BioMarin's plans to re-submit a BLA for Roctavian to the FDA by the end of September 2022; and the duration of the FDA's review procedure of BioMarin's BLA resubmission for Roctavian. These forward-looking statements are predictions and involve risks and uncertainties such that actual results may differ materially from these statements. These risks and uncertainties include, among others: the results and timing of current and planned preclinical studies and clinical trials of Roctavian; additional data from the continuation of the clinical trials of Roctavian, any potential adverse events observed in the continuing monitoring of the

participants in the clinical trials; the content and timing of decisions by the FDA, the EC and other regulatory authorities, including decisions to grant additional marketing registrations based on an EMA license; the content and timing of decisions by local and central ethics committees regarding the clinical trials; our ability to successfully manufacture Roctavian for the clinical trials and commercially; our ability to provide the additional data from currently ongoing Roctavian clinical studies to support the conversion from a CMA to a standard marketing authorization; and those and those factors detailed in BioMarin's filings with the Securities and Exchange Commission (SEC), including, without limitation, the factors contained under the caption "Risk Factors" in BioMarin's Quarterly Report on Form 10-Q for the quarter ended June 30, 2022 as such factors may be updated by any subsequent reports. Stockholders are urged not to place undue reliance on forward-looking statements, which speak only as of the date hereof. BioMarin is under no obligation, and expressly disclaims any obligation to update or alter any forward-looking statement, whether as a result of new information, future events or otherwise.

BioMarin® is a registered trademark of BioMarin Pharmaceutical Inc and ROCTAVIAN™ is a trademark of BioMarin Pharmaceutical Inc.

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