BioMarin Highlights New Results for Gene Therapy Valoctocogene Roxaparvovec at the 2017 American Society of Hemophilia (ASH) Meeting

New 1.5 Year Results Demonstrating 6e13 vg/kg Dose Achieved Sustained Factor VIII Levels within the Normal Range in Severe Hemophilia A for Most Patients
Up to One Year Results Demonstrating 4e13 vg/kg Dose Achieved Sustained Factor VIII Levels Approaching or within Lower End of Normal Range in Severe Hemophilia A for Most Patients
NEJM Publishes One-Year Data for 6e13 vg/kg Dose from Ongoing Phase 1/2 Study
New Pre-Clinical Results on Impact of Pre-Existing Immunogenicity to AAV on Vector Transduction by Valoctocogene Roxaparvovec, an AAV5-Based Gene Therapy Treatment for Hemophilia A
Early Results on Interim Analysis of Immunogenicity to the Vector Capsid and Transgene-Expressed Human FVIII in a Phase-1/2 Clinical Study of Valoctocogene Roxaparvovec, an AAV5-Mediated Gene Therapy for Hemophilia A

SAN RAFAEL, Calif., Dec. 11, 2017 /PRNewswire/ -- BioMarin Pharmaceutical Inc. (NASDAQ: BMRN) announced updates on valoctocogene roxaparvovec (formerly BMN 270), an investigational gene therapy treatment for severe hemophilia at ASH.

Efficacy Data with Valoctocogene Roxaparvovec 4e13 vg/kg Dose and 6e13 vg/kg Dose as Presented at ASH

With the 4e13 vg/kg dose, the three patients with the longest follow-up (at week 48) have Factor VIII activity levels that are in or near to the normal range with both median and mean values of 49%. Median annualized bleed and factor VIII use rates for the 4e13 vg/kg cohort were zero after Week 4 and when their Factor VIII activity rose above 5%. Mean annualized bleed and factor VIII use rates for the 4e13vg/kg cohort were 0.6 and 2.0, respectively. With the 6e13 vg/kg dose, at 78 weeks post infusion, the median and mean Factor VIII levels of the 6e13 vg/kg cohort were 90 and 89%, respectively. Median annualized bleed and factor VIII use rates for the 6e13 vg/kg were zero after Week 4. Mean annualized bleed and factor VIII use rates for the 6e13 vg/kg cohort were 0.5 and 6.1, respectively. Please see full release issued December 9, 2017 here for details.

"The confluence of new medicines and advanced treatment approaches for hemophilia has created an unprecedented opportunity to improve outcomes for patients today and in the future," said Hank Fuchs, M.D., President, Worldwide Research and Development at BioMarin. "We are very encouraged that our findings to date suggest a one-time infusion of valoctocogene roxaparvovec has the potential to eliminate bleeds, the need for exogenous factor VIII infusions and achieve FVIII levels in the normal range for patients with severe hemophilia A, with a very acceptable safety profile. We are entering a new era for the treatment of severe hemophilia and look forward to advancing an innovative therapeutic platform for our patients."

***New England Journal of Medicine* Publishes 1 Year Data on 6e13 vg/kg Dose Data**

The company also announced that the *New England Journal of Medicine* (NEJM) published an independent, peer-reviewed article on the ongoing Phase 1/2 study of valoctocogene roxaparvovec, an investigational gene therapy, in men with severe hemophilia A. The article assessed the safety and efficacy of valoctocogene

roxaparvovec at the 6e13 dose, after 52 weeks.

The NEJM article, "AAV Gene Transfer in Patients with Severe Hemophilia A," reported "sustained normalization" of Factor VIII activity over the 52-week period for six of seven study participants who received the 6e13 vg/kg dose of valoctocogene roxaparvovec. In addition, all seven participants demonstrated stabilization of hemostasis and a "profound" reduction in Factor VIII use. Safety findings were limited to elevations in liver function tests, noting the relatively small sample size. For additional safety data, see the *Safety* section below in the press release.

Abstract (poster) #3332, titled, "Impact of Pre-Existing Immunogenicity to AAV on Vector Transduction by BMN 270, an AAV5-Based Gene Therapy Treatment for Hemophilia A"

As presented at ASH on December 10, the objective of this study was to determine the comparative pharmacodynamics of valoctocogene roxaparvovec when given as a single intravenous bolus injection to cynomolgus monkeys with varying baseline anti-AAV5 total antibody (TAb) levels and transduction inhibition (TI) titers. The results demonstrated no evidence for decreased FVIII expression in animals with non-antibody based transduction inhibition, while baseline AAV5 antibody positive animals had a range of FVIII expression. These data suggest a reasonable likelihood that valoctocogene roxaparvovec may be efficacious for individuals with baseline anti-AAV5 TAb. Importantly, the threshold for a positive AAV5 TAb assay result may be lower than baseline anti-AAV5 TAb levels that impact efficient vector transduction. These data support the initiation of the Phase 1/2 BMN 270-203 study, which will evaluate the safety and efficacy of valoctocogene roxaparvovec in severe hemophilia A subjects who have various baseline anti-AAV5 TAb levels.

Abstract (poster) #4611, titled, "Interim Analysis of Immunogenicity to the Vector Capsid and Transgene-Expressed Human FVIII in a Phase-1/2 Clinical Study of BMN 270, an AAV5-Mediated Gene Therapy for Hemophilia A"

As presented at ASH on December 11, this study analyzed both the cellular and humoral immune responses to the AAV5 capsid and the hFVIII transgene product in subjects in the Phase 1/2 study BMN 270-201 with valoctocogene roxaparvovec. No FVIII inhibitor (by Nijmegen Bethesda assay) or sustained non-neutralizing FVIII TAb responses have been detected in any valoctocogene roxaparvovec treated patients. As anticipated, all patients developed an antibody specific for the AAV5 capsid by week 8 post-infusion. No significant cellular immune responses specific for the AAV5 capsid or FVIII were detected, which is distinct from results from non-AAV5 vector studies that correlated capsid immune responses to temporal elevations in alanine transaminase levels as well as loss of factor activity. The absence of adaptive immune responses observed to valoctocogene roxaparvovec that impacted clinical safety or efficacy suggest that certain immune responses may be specific to AAV serotypes and are not a class effect.

Valoctocogene Roxaparvovec Safety

Overall, valoctocogene roxaparvovec has been well-tolerated by patients across all doses, including the two patients who received the lowest doses of 6e12 and 2e13 vg/kg, respectively. 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 alanine aminotransferase (ALT) elevation (11 patients, 73%); arthralgia (9 patients, 60%); aspartate aminotransferase elevation (8 patients, 53%); headache (7 patients, 47%); back pain, fatigue and upper respiratory tract infection (5 patients, 33%). 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 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.

Regulatory Status

The U.S. Food and Drug Administration (FDA) granted valoctocogene roxaparvovec Breakthrough Therapy Designation. The FDA's Breakthrough Therapy Designation program is intended to facilitate and expedite development and review of new drugs to address unmet medical need in the treatment of a serious condition. To qualify for Breakthrough Therapy Designation, preliminary clinical evidence must show that that the drug may demonstrate substantial improvement over existing therapies.

The European Medicines Agency (EMA) has granted access to its Priority Medicines (PRIME) regulatory initiative for valoctocogene roxaparvovec. To be accepted for PRIME, an investigational therapy has to show its potential to benefit patients with unmet medical needs based on early clinical data. PRIME focuses on medicines that may offer a major therapeutic advantage over existing treatments, or benefit patients with no treatment options. These medicines are considered priority medicines within the European Union (EU).

BioMarin's valoctocogene roxaparvovec has also received orphan drug designation from the FDA and EMA for the treatment of severe hemophilia A. The Orphan Drug Designation program is intended to advance the evaluation and development of products that demonstrate promise for the diagnosis and/or treatment of rare diseases or conditions.

Gene Therapy Manufacturing

BioMarin has constructed one of the largest gene therapy manufacturing facilities in the world, which is located in Novato, California. Good Manufacturing Practices (GMP) production of valoctocogene roxaparvovec has commenced and will support clinical development activities and anticipated commercial demand. This facility is capable of supporting approximately 2,000 patients per year, and the production process was developed in accordance with International Conference on Harmonisation guidance for Pharmaceuticals for Human Use facilitating worldwide registration with health authorities.

About Hemophilia A

Hemophilia A, also called Factor VIII (FVIII) deficiency or classic hemophilia, is a 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. As an X-linked disorder, hemophilia A mostly affects males, occurring in approximately 1 in 5,000 male births. People living with the disease are not able to form blood clots efficiently and are at risk for excessive bleeding from modest injuries, potentially endangering their life. People with severe hemophilia often bleed spontaneously into their muscles or joints. The standard of care for the 43% of hemophilia A patients who are severely affected, is a prophylactic regimen of Factor VIII infusions three times per week. Even with prophylactic regimens, many patients still experience microbleeds and spontaneous bleeding events that result in progressive joint damage.

About BioMarin

BioMarin is a global biotechnology company that develops and commercializes innovative therapies for patients with serious and life-threatening rare and ultra-rare genetic diseases. The company's portfolio consists of six commercialized products and multiple clinical and pre-clinical product candidates. For additional information, please visit www.biomarin.com. Information on BioMarin's website is not incorporated by reference into this press release.

Forward Looking Statement

This press release contains forward-looking statements about the business prospects of BioMarin Pharmaceutical Inc., including without limitation, statements about the development of BioMarin's valoctocogene roxaparvovec program generally, the impact of valoctocogene roxaparvovec gene therapy for treating patients with severe hemophilia A, the potential for valoctocogene roxaparvovec to bring Factor VIII levels to normal and to reduce or eliminate bleeds, the planned Phase 3 studies, the planed Phase 1/2 study, or other possible future clinical studies of valoctocogene roxaparvovec. 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: results and timing of current and planned preclinical studies and clinical trials of valoctocogene roxaparvovec, including final analysis of the above interim data; any potential adverse events observed in the continuing monitoring of the patients in the Phase 1/2 trial; the content and timing of decisions by the U.S. Food and Drug Administration, the European Commission and other regulatory authorities; the content and timing of decisions by local and central ethics committees regarding the clinical trials; our ability to successfully manufacture the product candidate for the preclinical and clinical trials; and those other risks detailed from time to time under the caption "Risk Factors" and elsewhere in BioMarin's Securities and Exchange Commission (SEC) filings, including BioMarin's Quarterly Report on Form 10-Q for the quarter ended September 30, 2017, and future filings and reports by BioMarin. BioMarin undertakes no duty or obligation to update any forward-looking statements contained in this press release as a result of new information, future events, or changes in its expectations.

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