# BioMarin Announces that Phase 3 Cohort of Valoctocogene Roxaparvovec, Gene Therapy Study in Severe Hemophilia A Met Pre-Specified Criteria for Regulatory Submissions in the U.S. and Europe

***Timing of Regulatory Submissions to Be Determined in 3Q 2019***

***Conference Call and Webcast to be Held Tuesday, May 28, 2019 at 8:00 AM Eastern***

SAN RAFAEL, Calif., May 28, 2019 /PRNewswire/ -- BioMarin Pharmaceutical Inc. (NASDAQ: BMRN) announced today that its investigational gene therapy, valoctocogene roxaparvovec, for adults with severe hemophilia A achieved pre-specified clinical criteria for regulatory review in the U.S. and Europe. As of May 28, 2019, eight patients in the 20-patient cohort of the Phase 3 GENEr8-1 study achieved Factor VIII levels of 40 international units per deciliter (IU/dL), or more, at 23 to 26 weeks, meeting the pre-specified criteria for Factor VIII activity levels. The company will meet with the Food and Drug Administration (FDA) and European Medicines Agency (EMA) to review the phase 3 data and the other elements of a submission and intends to announce the timing for its planned marketing applications in 3Q 2019.

## Topline Data Results

As of the April 30, 2019 data cutoff, between weeks 23 to 26, in a cohort of the Phase 3 GENEr8-1 study of valoctocogene roxaparvovec dosed at 6e13 vg/kg, seven of 16 study participants reached or exceeded the pre-specified Factor VIII levels of 40 international units per deciliter using the chromogenic substrate (CS) assay. Subsequent to the April 30 cutoff, one additional participant met that criteria, bringing the total to eight participants.

For the 16 patients who had reached week 26 by the April 30 cutoff since administration of valoctocogene roxaparvovec, the estimated median Annual Bleed Rate (ABR) was zero and the estimated mean ABR was 1.5, representing a reduction of 85% from baseline levels where all patients were on standard of care prophylaxis. In addition, there was an 84% reduction in median annualized Factor VIII usage and a 94% reduction in mean FVIII usage annualized between week 5 and 26. In the 23 to 26 week time period the mean Factor VIII level using the CS assay was 36 (SD=28) IU/dL and the median was 33 IU/dL.

"Reaching this pre-specified clinical endpoint is an important milestone that brings us one step closer to a potential regulatory submission in both the U.S. and Europe for valoctocogene roxaparvovec to treat adults with severe hemophilia A," said Hank Fuchs, M.D., President of Worldwide Research and Development at BioMarin. "Our discussions with the FDA and EMA underscore the high level of unmet need in the hemophilia community, and we look forward to continuing our productive dialogue on the submissions."

**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 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.

**Conference Call and Webcast to be Held May 28, 2019 at 8:00 AM Eastern Time**

Interested parties may access a live video webcast that will include audio and slides of the presentations via the investor section of the BioMarin website. A replay of the meeting will be archived on the site for one week.

For those who choose not to listen and view the event via webcast, dial-in information for the audio portion of the webcast can be accessed using:

U.S. / Canada Dial-in Number: (866) 502-9859
International Dial-in Number: (574) 990-1362
Conference ID: 2295086

Replay Dial-in Number: (855) 859-2056
Replay International Dial-in Number: (404) 537-3406
Conference ID: 2295086

**Registrational Studies Underway; GENEr8-1 to Evaluate Superiority**

The global Phase 3 program includes two studies with valoctocogene roxaparvovec, one with the 6e13 vg/kg dose (GENEr8-1) and one with the 4e13 vg/kg dose (GENEr8-2). With the goal of evaluating superiority of valoctocogene roxaparvovec to the current standard of care, prophylactic therapy, the sample size of the GENEr8-1 study is approximately 130 total participants. The study is powered to evaluate superiority to the current standard of care. Enrollment completion in the newly amended GENEr8-1 study is expected in the third quarter of 2019.

GENEr8-2, the ongoing Phase 3 study with the 4e13 vg/kg dose, remains unchanged with an N=40. The GENEr8-2 study is expected to complete enrollment one to two quarters after GENEr8-1 in 2019.

BioMarin now has six clinical studies underway in its comprehensive gene therapy program for the treatment of severe hemophilia A. In addition to the two global Phase 3 studies GENEr8-1 and GENEr8-2, the Company recently began a Phase 1/2 Study with the 6E13kg/vg dose of valoctocogene roxaparvovec in approximately 10 participants with pre-existing AAV5 antibodies. Two additional and separate studies, one to study seroprevalence in people with severe hemophilia A and one non-interventional study to determine baseline characteristics in people with hemophilia A, are ongoing around the world. Participants in the Phase 1/2 dose escalation study will continue to be monitored as part of the global program underway.

Valoctocogene roxaparvovec investigational product from BioMarin's commercial scale manufacturing facility will be used in all BioMarin interventional studies going forward. Product to support the additional participants in the GENEr8-1 has been produced and is immediately available.

**Valoctocogene Roxaparvovec Safety**

Overall, valoctocogene roxaparvovec has been well-tolerated by the 22 participants in the Phase 3 cohort at the 6e13 vg/kg dose. No participants developed inhibitors to Factor VIII, and no participants withdrew from the study. The most common adverse events (AEs) were alanine aminotransferase (ALT) elevation (17 participants, 77.3%), nausea (11 participants, 50%), headache (10 participants, 45.5%), fatigue (9 participants, 40.9%), arthralgia (8 participants, 36.4%), AST elevation (8 participants, 36.4%), nasopharyngitis (7 participants, 31.8%), back pain (6 participants, 27.3%), and oropharyngeal pain (5 participants, 22.7%). Three subjects experienced serious adverse events (SAEs) (13.6%); two SAEs were related to infusion reactions, one SAE of gastroenteritis was unrelated to treatment.

**Gene Therapy Manufacturing**

BioMarin has constructed one of the first gene therapy manufacturing facilities of its kind in the world, which is located in Novato, California. Good Manufacturing Practices (GMP) production of valoctocogene roxaparvovec has commenced, and this manufacturing facility will support pivotal clinical development activities and anticipated commercial demand, if valoctocogene roxaparvovec is approved. This facility is capable of supporting approximately 4,000 doses 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. In 2018, the International Society for Pharmaceutical Engineering (ISPE) selected the Company's gene therapy manufacturing facility as the Facility of the Year Category Winner for Project Execution.

**About Hemophilia A**

People living with hemophilia A lack enough FVIII protein to help their blood clot and are at risk for painful, potentially life-threatening bleeds from even

modest injuries.  Additionally, people with severe hemophilia A often experience painful, spontaneous bleeds into their muscles or joints.  The standard of care for the 43 percent of individuals with hemophilia A who are severely affected is a prophylactic regimen of Factor VIII infusions administered intravenously two to three times per week.  Despite these regimens, many people continue to experience 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 (FVIII) 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 is born with Hemophilia A.

**About BioMarin**

BioMarin is a global biotechnology company that develops and commercializes innovative therapies for serious and life-threatening rare and ultra-rare genetic diseases. The Company's portfolio consists of seven 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 Statements**

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 possibility of an accelerated and/or conditional filing and approval by the FDA or EMA, respectively; the impact of valoctocogene

roxaparvovec gene therapy for treating patients with severe hemophilia A, the potential for valoctocogene roxaparvovec to reduce or eliminate bleeds, reduce the number of Factor VIII infusions, improve the quality of life and the ongoing clinical programs generally. 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 and additional data from the continuation of these trials; any potential adverse events observed in the continuing monitoring of the patients in the clinical trials; the content and timing of decisions by the FDA, the EMA 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 Annual and quarterly Reports on Forms 10-K and 10-Q, 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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