BioMarin Announces New England Journal of Medicine Publishes 3 Years of Follow-up Data in Phase 1/2 Study of Valoctocogene Roxaparvovec Gene Therapy for Hemophilia A

Single Dose Resulted in Sustained Mean Reduction of 96% in Bleed Rates at 6e13 vg/kg Dose in Third Year

Completely Eliminated Prophylactic Factor VIII Use in 6e13 vg/kg and 4e13 vg/kg Doses

2nd Publication in NEJM on Valoctocogene Roxaparvovec

SAN RAFAEL, Calif., Jan. 2, 2020 /PRNewswire/ --BioMarin Pharmaceutical Inc. (NASDAQ: BMRN) announced today that the New England Journal of Medicine (NEJM) published an independently peer-reviewed article on up to three years of data from an ongoing Phase 1/2 study to evaluate safety and efficacy of investigational AAV gene therapy, valoctocogene roxaparvovec, for severe hemophilia A. This is the second article published by the NEJM on valoctocogene roxaparvovec.

The NEJM article, "Multiyear Follow-up of AAV5-hFVIII-SQ Gene Therapy for Hemophilia A", demonstrated that a single infusion of valoctocogene roxaparvovec "resulted in sustained, clinically relevant benefit, as measured by a substantial reduction in annualized rates of bleeding events and complete cessation of prophylactic factor VIII use in all 13 participants who had received 4e13vg/kg or 6e13 vg/kg."

Twelve of these participants also experienced a full resolution of target joints. Recurrent bleeding into the same joint results in a "target joint" and is defined as three bleeds into the same joint within a 6-month period. Bleeding into joints causes pain and ultimately results in impairment of the joint and permanent damage (hemophilic arthropathy).[i] Resolution of a target joint is when there have been less than two bleeds into the joint within a consecutive 12-month period.[ii]

In addition to reporting safety and efficacy, the article contributes to a greater understanding of the variability observed in gene therapy studies and provides insights into mechanisms of DNA persistence and durability.

The article noted that the most common adverse event was a transient elevation in alanine aminotransferase (ALT) levels with no indications of ongoing liver damage, and that no participants withdrew from the study. For additional safety data, see *Safety*

section in press release.

"With each passing year, we come to appreciate further the transformation in patient lives that may be possible with gene therapy. As pioneers in the field, we are proud to sponsor research that is published in leading scientific journals so that we and the scientific community can learn together about how to characterize long-term benefits and ultimately optimize patient outcomes," said Hank Fuchs, M.D., President, Worldwide Research and Development at BioMarin. "We look forward to providing a four year update at a scientific congress in the middle of this year, during which we'll also provide a third year of follow up after lower levels of expression were achieved using a lower dose."

"These data are critical in helping the scientific and medical communities understand this pioneering technology. With three years of data, we know more about valoctocogene roxaparvovec than any other gene therapies in development for hemophilia A," said Professor John Pasi, M.B., Ch.B., Ph.D., from Barts and the London School of Medicine and Dentistry; the lead author of this NEJM publication, chief investigator for the valoctocogene roxaparvovec Phase 1/2 study, and a principal investigator for the Phase 3 study. "As a treating physician, I am excited about the potential of the field of gene therapy to make a meaningful difference in the lives of people with hemophilia A."

Annualized Bleed Rates and Factor VIII Levels in the 6e13 vg/kg Dose Cohort

Three years after administration of valoctocogene roxaparvovec at the 6e13 vg/kg dose among the seven participants, the median number of annualized treated bleeding events was 0. The mean annualized bleeding rate decreased by 96% from a mean ($\pm$SD) of 16.3$\pm$15.7 events per year (median, 16.5 events per year) at baseline (on prophylactic standard of care) to 0.7$\pm$1.6 events per year (median, 0.0 events per year) in year 3.

In the year before study entry, only one participant who was receiving prophylaxis was free from breakthrough bleeding events that necessitated additional Factor VIII treatment. During year 3, a total of six participants (86%) were free from bleeding events. In the first, second and third years, 71%, 86% and 86%, respectively, of study participants had zero bleeds requiring Factor VIII infusions compared to 17% who had zero bleeds requiring Factor VIII infusions in the year prior to study entry. All the participants experienced full resolution of target joints.

In addition, using the chromogenic substrate (CS) assay expressed as an international unit per deciliter (IU/dL) Factor VIII levels sustained over a three-year period were

sufficient to achieve hemostatic efficacy. Factor VIII expression may have entered a plateau phase as the rate of decline has substantially slowed, which could be indicative of durable, long-term expression. At the end of the first, second and third years, post-infusion, mean Factor VIII activity level were 64, 36 and 33 IU/dL respectively. The median Factor VIII activity levels at the end of the first, second and third years were 60, 26 and 20 IU/dL respectively.

Annualized Use of Exogenous Factor VIII in the 6e13 vg/kg Dose Cohort

The median use of exogenous factor VIII at the 6e13 vg/kg dose was reduced from 138.5 infusions per year to zero infusions per year in year 3. In the year before study entry, the mean annualized number of factor VIII infusions per participant was 136.7±22.4; at the end of year 3, the mean annualized use of exogenous factor VIII decreased by 96% to a mean of 5.5±9.4 infusions. 98% of the factor VIII infusions that occurred later than 5 weeks post-administration were reported in association with total knee-replacement surgeries in two participants, which were performed due to preexisting chronic hemophilic arthropathy.

A total of 11 treated bleeding events were reported in this cohort after week 5, with 10 of these events occurring in one participant, who had the lowest factor VIII expression after administration.

Safety Summary

Overall, valoctocogene roxaparvovec continues to have a favorable safety profile and has been well-tolerated by participants across all doses in the Phase 1/2 and Phase 3 studies. No participants developed inhibitors to Factor VIII, and no participants withdrew from the study. All participants have remained off Factor VIII prophylaxis. Corticosteroid use was transient with no long-lasting clinical sequelae. No participants have developed thrombotic events. The most common adverse events associated with valoctocogene roxaparvovec across studies include transient infusion associated reactions and transient, asymptomatic, and mild to moderate rise in the levels of certain proteins and enzymes measured in liver function tests.

About Hemophilia A

People living with hemophilia A lack enough 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 often

experience painful, spontaneous bleeds into their muscles or joints. Individuals with the most severe form of hemophilia A make up approximately 43 percent of the hemophilia A population. The standard of care for such individuals with hemophilia A is a prophylactic regimen of replacement Factor VIII infusions administered intravenously up to two to three times per week or 100 to 150 infusions per year. 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 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.

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 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 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, or the planned updates of the Phase 1/2 study including the Company's plan to share four years of data from this study mid-year. 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, 2019, 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.

BioMarin® is a registered trademark of BioMarin Pharmaceutical Inc.

[i] *Joint Health in Hemophilia: Latest Approaches and Advances (CME):* Doris Quon, MD, PhD, Released: 2/5/2019, https://www.medscape.org/viewarticle/908267(as of 1/1/2020).

[ii] *Definitions in hemophilia: communication from the SSC of the ISTH*V. S. Blanchette, et al for the Subcommittee on Factor VIII, Factor IX and Rare Coagulation Disorders: 24 July 2014, https://doi.org/10.1111/jth.12672 (as of 1/1/20: https://onlinelibrary.wiley.com/doi/full/10.1111/jth.12672)

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