BioMarin Announces 6 Presentations at American Society of Gene and Cell Therapy (ASGCT) Virtual 2021 Annual Meeting

Research Findings are Part of the Largest and Longest Development Program for any Gene Therapy in Hemophilia A and Advance the Scientific Understanding of AAV5 Gene Therapy

SAN RAFAEL, Calif., May 12, 2021 /PRNewswire/ -- BioMarin Pharmaceutical Inc. (NASDAQ: BMRN) today announced three oral and three poster presentations on valoctocogene roxaparvovec, an investigational gene therapy for the treatment of adults with severe hemophilia A at the American Society of Gene and Cell Therapy (ASGCT) Virtual 2021 Annual Meeting being held May 11-14. These six presentations advance the scientific understanding of the potential of valoctocogene roxaparvovec to treat people with hemophilia A.

"BioMarin is committed to furthering our scientific understanding of gene therapy through our experience developing valoctocogene roxaparvovec. This foundation of knowledge will help to inform the development of other gene therapies in our pipeline. The studies presented at ASGCT illustrate our continued quest to define who responds to treatment, why, and for how long. Vector catabolism remains the leading hypothesis as to why Factor VIII expression evolves over time, highlighting pathways to improve patient outcomes," said Lon Cardon, Ph.D., Senior Vice President, Chief Scientific Strategy Officer at BioMarin. "Our presentations at ASGCT extend our nearly decade-long experience in AAV scientific and clinical research to improve our understanding of the critical features of vectors, promoters, pharmacologic agents, and manufacturing technologies to help us deliver potentially transformative treatments to people with rare genetic disease."

The oral presentation, *Investigating Mechanisms of Variability of AAV5-hFVIII-*

SQ Expression in Mice, provide new insights into inter-individual differences in Factor VIII expression of regulatory molecules involved in transduction, transcription and protein folding/secretion, as well as advance the understanding of factors that may impact variability in transgene expression. BioMarin is conducting multiple ongoing in vitro and in vivo studies to further investigate the mechanistic drivers of AAV5 gene therapy variability.

The oral presentation, *Long-Term Expression Comparison of Adeno-Associated Virus (AAV) Vector Produced in HEK293 vs Sf Cell Lines*, compares the durability of transgene expression in mice using vectors produced in mammalian cell production systems or baculovirus—Spodoptera frugiperda (Sf) insect-cell systems—and showed comparable long-term durability of transgene expression by week 12 through week 57 with no difference between HEK293- vs Sf-produced groups.

The poster presentation, *Rare Genomic Integrations of AAV5-hFVIII-SQ Occur without Evidence of Clonal Activation or Gene-Specific Targeting*, showed that in liver samples from non-human primates, 13 or 26 weeks after vector administration, the vast majority of AAV5-FVIII-SQ vector or valoctocogene roxaparvovec (>99.9%) showed no signs of integration, consistent with a predominantly episomal presence. Rare vector integration events occurred on average in less than 1 in 600 liver cells, which is in line with expectations for AAV vectors and several orders of magnitude lower than the natural mutation rate in the general population. There was no evidence of clonal expansion, suggesting that individual integration sites were restricted to single cells or small groups of progeny cells. BioMarin supports continuous scientific evaluations to better characterize integration profiles across AAV gene therapy products.

BioMarin's presentations at ASGCT include:

Platform Presentations

Investigating Mechanisms of Variability of AAV5-hFVIII-SQ Expression in Mice
Bridget Yates
BioMarin Pharmaceutical Inc., Novato, CA, USA
Wednesday, May 12 · 6:30 – 6:45 pm

Long-Term Expression Comparison of Adeno-Associated Virus (AAV) Vector Produced in HEK293 vs Sf Cell Lines
Britta Handyside, PhD
BioMarin Pharmaceutical Inc., Novato, CA, USA
Wednesday, May 12 · 7:15 – 7:30 pm

Lack of Germline Transmission in Male Mice Following Administration of AAV5-hFVIII-SQ, an Investigational Gene Therapy for Hemophilia A
Cheng Su, PhD
BioMarin Pharmaceutical Inc., Novato, CA, USA
Friday, May 14 · 1:00 – 1:15 pm

Poster Sessions

Poster #	Title & Authors
338	The Effect of Prophylactic Corticosteroid Treatment on Adeno-Associated Virus (AAV)-Mediated Gene Expression Handyside B, Zhang L, Yates B, Xie L, Kaplowitz B, Gorostiza O, Murphy R, Fredette N, Baridon B, Ngo K, Siso S, Agrawal V, Cortesio C, Akeefe H, Woloszynek J, Zhang W, Su C, Colosi P, Bullens S, Veres G, Bunting S, Fong S
	Ultra-Sensitive AAV Capsid Detection by Immunocapture-Based

892	Ultra-Sensitive AAV Capsid Detection by Immunocapture-Based Quantitative Polymerase Chain Reaction Following Factor VIII Gene Transfer Sandza K, Clark A, Koziol E, Akeefe H, Yang F, Holcomb J, Patton K, Hammon K, Mitchell N, Wong W, Zoog S, Kim B, Henshaw J, Vettermann C
895	Rare Genomic Integrations of AAV5-hFVIII-SQ Occur without Evidence of Clonal Activation or Gene-Specific Targeting Sullivan L, Zahn M, Gil Farina I, Kasprzyk T, O'Neill C, Eggan K, Zoog S, Veres G, Schmidt M, Vettermann C

Regulatory Status

In Europe, BioMarin plans to submit a Marketing Authorization Application (MAA) for valoctocogene roxaparvovec for the treatment of severe hemophilia A with one-year results from the Phase 3 GENEr8-1 study to the European Medicines Agency (EMA) in June 2021.

In the United States, BioMarin plans to submit two-year follow-up safety and efficacy data on all study participants from the GENEr8-1 study to support the benefit/risk assessment of valoctocogene roxaparvovec. BioMarin is targeting a Biologics License Application (BLA) submission in the second quarter of 2022 assuming favorable study results, followed by an expected six-month review procedure by the FDA.

The FDA granted Regenerative Medicine Advanced Therapy (RMAT) designation to valoctocogene roxaparvovec in March 2021. RMAT is an expedited program intended to facilitate development and review of

regenerative medicine therapies, such as valoctocogene roxaparvovec, that are intended to address an unmet medical need in patients with serious conditions. The RMAT designation is complementary to Breakthrough Therapy Designation, which the Company received in 2017, allowing early, close, and frequent interactions with the FDA.

In addition to the RMAT Designation and Breakthrough Therapy Designation, BioMarin's valoctocogene roxaparvovec also has 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.

Robust Clinical Program

BioMarin has multiple clinical studies underway in its comprehensive gene therapy program for the treatment of severe hemophilia A. In addition to the global Phase 3 study GENEr8-1 and the ongoing Phase 1/2 dose escalation study, the Company is actively enrolling participants in a Phase 3b, single arm, open-label study to evaluate the efficacy and safety of valoctocogene roxaparvovec at a dose of 6e13 vg/kg with prophylactic corticosteroids in people with hemophilia A. The Company is running a Phase 1/2 Study with the 6e13kg/vg dose of valoctocogene roxaparvovec in approximately 10 participants with pre-existing AAV5 antibodies, as well as another Phase 1/2 Study with the 6e13 vg/kg dose of valoctocogene roxaparvovec in people with hemophilia A with active or prior FVIII inhibitors.

Gene Therapy Manufacturing

BioMarin has leveraged its knowledge and experience in manufacturing

complex biological products to design, construct and validate a state-of-the-art vector production facility in Novato, California. This facility is the site of production for both valoctocogene roxaparvovec and BMN 307, an investigational gene therapy to treat Phenylketonuria. Manufacturing capabilities are an essential driver for BioMarin's gene therapy programs and allows the Company to control quality, capacity, costs and scheduling enabling rapid development. Production of gene therapies with a commercial ready process at scale reduces risk associated with making process changes later in development and may speed overall development timelines significantly.

Ongoing process development efforts and experience gained at commercial scale have led to improvements in productivity and operational efficiency. The ability to scale out the facility with additional equipment combined with the improvements in productivity result in a doubling of overall potential capacity to 10,000 doses per year, combined for both products, depending on final dose and product mix. This improvement in productivity is anticipated to meet potential commercial and clinical demand for both valoctocogene roxaparvovec and BMN 307 well into the future.

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 (FVIII 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 (FVIII 1-5%) or mild (FVIII 5-40%) disease show a much-reduced propensity to bleed. The standard of care for individuals with severe 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 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.

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 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 Statements

This press release contains forward-looking statements about the business prospects of BioMarin Pharmaceutical Inc., including without limitation, statements about the potential of valoctocogene roxaparvovec to treat people with hemophilia A, the foundation of knowledge from these studies will help to inform the development of other gene therapies in our pipeline, , our experience in AAV scientific and clinical research helping us to deliver potentially transformative treatments, , the Company's plans to submit an MAA to EMA in June 2021, the Company's plans to submit two-year follow-up safety

and efficacy data on all study participants from the GENEr8-1 study to the FDA, the Company targeting a BLA submission to the FDA in the second quarter of 2022 followed by an expected six-month review procedure by the FDA and statements about the overall potential capacity of our vector production manufacturing facility in Novato to produce 10,000 doses per year, depending on final dose and product mix, and the anticipation that this capacity will meet potential commercial and clinical demand for both valoctocogene roxaparvovec and BMN 307 well into the future. 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 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 without limitation, BioMarin's Quarterly Report on Form 10-Q for the quarter ended March 31, 2021, as such factors may be updated by any subsequent reports. 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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