BioMarin Announces Oral Presentation at International Society on Thrombosis and Haemostasis (ISTH) 2021 Virtual Congress with 5 Years of Clinical Data from Ongoing Phase 1/2 Study of Valoctocogene Roxaparvovec in Adults with Severe Hemophilia A, Demonstrating Continued, Durable Clinical Benefit

Sustained Clinical Hemostatic Efficacy Observed in Study Participants with Longest Duration of Clinical Experience for any Gene Therapy in Hemophilia A

Phase 1/2 and Subset of Pivotal GENEr8-1 Studies Demonstrate Consistent Bleed Control following Treatment with Valoctocogene Roxaparvovec

All Study Participants in 6e13 vg/kg and 4e13 vg/kg Dose Cohorts Remain off Factor VIII Prophylactic Therapy

SAN RAFAEL, Calif., July 21, 2021 /PRNewswire/ -- BioMarin Pharmaceutical Inc. (NASDAQ: BMRN) announced today new data for valoctocogene roxaparvovec, an investigational gene therapy treatment for adults with severe hemophilia A, from its open-label Phase 1/2 study during an oral presentation at the International Society on Thrombosis and Haemostasis (ISTH) 2021 Virtual Congress.

Five-year and four-year post-treatment follow-up of the 6e13 vg/kg and 4e13 vg/kg cohorts, respectively, shows a sustained treatment benefit of valoctocogene roxaparvovec. All participants in both cohorts remain off prophylactic Factor VIII treatment.

Annualized Bleed Rate

The 6e13 vg/kg dose cohort of the Phase 1/2 study (N=7), with a mean follow-up of 266.1 weeks (5.1 years), showed that a single dose of valoctocogene roxaparvovec after week 4 reduced mean ABR by 95% from 16.3 (median 16.5) at baseline to 0.8 (median 0.0) bleeding episodes per year among the 6 participants previously treated with FVIII prophylaxis. In year 5, 86% (6 of 7) of study participants in the 6e13 vg/kg dose cohort had no treated bleeds.

The 4e13 vg/kg dose cohort of the Phase 1/2 study (N=6), with a mean follow-up of 218.6 weeks (4.2 years) showed that a single dose of valoctocogene roxaparvovec reduced mean ABR by 92% from 12.2 (median 8.0) at baseline to 1.0 (median 0.5) bleeding episodes per year. In year 4, 50% (3/6) of study participants in the 4e13 vg/kg dose

cohort had no treated bleeds.

Factor VIII Utilization

In the 6e13 vg/kg dose cohort after week 4, the mean annualized Factor VIII utilization was reduced by 96% from 135.6 (median 136.5) to 5.2 (median 0.1) infusions per year among the six participants previously treated with FVIII prophylaxis. (This excludes one study participant receiving on-demand Factor VIII prophylaxis at baseline.)

In the 4e13 vg/kg dose cohort after week 4, the mean annualized Factor VIII utilization was reduced by 95% from 142.8 (median 155.8) to 7.8 (median 1.4) infusions per year. During follow-up, in both cohorts, exogenous Factor VIII was used as treatment for bleeding, surgery or procedures, and as one-time prophylaxis.

Factor VIII Expression and Rate of Change Over Time Comparable in Phase 1/2 and Pivotal Phase 3 Studies

For the 6e13 vg/kg and 4e13 vg/kg cohorts, study participants continued to have clinically meaningful levels in endogenous Factor VIII expression (Table 1). Mean Factor VIII activity levels over five and four years, respectively, support the observed reductions in bleed rates and annualized Factor VIII usage.

Table 1: Factor VIII Activity Levels of 4e13 and 6e13 vg/kg dose cohorts for 4 and 5 Years respectively as measured by CS and OS assays

Factor VIII Activity, IU/dL	**Chromogenic Substrate Assay** **Mean (SD)** **Median**	**One-Stage Assay** **Mean (SD)** **Median**
4e13 vg/kg Dose Cohort at 4 Years (N=6)	5.6 (5.6) 4.8	9.5 (7.0) 7.5

6e13 vg/kg Dose Cohort at 5 Years (N=7)	11.6 (12.2) 8.2	18.7 (17.5) 15.7

Factor VIII activity levels for participants in the 6e13 and 4e13 vg/kg vg/kg dose cohorts, was highest in year 1, and the rate of Factor VIII decline in years 4 and 5 were commensurate with that observed in previous years. Earlier, results from the pivotal Phase 3 GENEr8-1 study were presented at ISTH. The mean Factor VIII activity from a subset of the population that had been dosed at least two years prior to the data cut date (N=17) falls between Factor VIII activity of the 6e13 and 4e13 vg/kg dose cohorts in the Phase 1/2 study and is of help in understanding the potential future trajectory of Factor VIII activity in the GENEr8-1 study. In the subset of the GENEr8-1 study that had been dosed at least two years prior to the data cut date, Factor VIII expression declined from a mean of 42.2 (median 23.9) IU/dL at the end of year one to 24.4 (median 14.7) IU/dL at the end of year two with continued hemostatic efficacy as measured by the chromogenic substrate (CS) assay.

Individual Participant ABR, Factor VIII Infusion Rate, and Factor VIII Activity

In the 6e13 and 4e13 vg/kg dose cohorts, after week 4, all participants continued to experience a reduction in ABR compared to their baseline values, even participants with low Factor VIII activity. No participants chose to resume routine prophylaxis.

In the most recent year of observation in the 6e13 vg/kg dose cohort, six of the seven participants were in the mild to moderate hemophilia range, and one participant was below the lower limit of quantification as measured by the CS assay. Measuring with the one-stage (OS) assay, one participant was in the non-hemophilic range, four were in the mild range, and one was in the moderate range.

In the 4e13 vg/kg dose cohort, four of the six participants were in the mild to moderate hemophilia range, and two participants were below the lower limit of quantification as measured by the CS assay. Measuring with the OS assay, all six participants were in the mild to moderate range.

"The consistent and impressive bleed control in the majority of the study participants out to five years in this study, which is the longest duration of clinical experience for any gene therapy in hemophilia A, which increases our understanding of the interplay between Factor VIII expression, ABR, and Factor VIII infusion rate as it relates to hemostatic efficacy," said Professor Michael Laffan, faculty of Medicine, Department of Immunology and Inflammation at Imperial College London, Director of the Hammersmith Hospital Haemophilia Centre, and Chief Investigator for the valoctocogene roxaparvovec Phase 1/2 study. "These data show that most of the study participants have not had a bleed or had to infuse Factor VIII in the last five years after one infusion of valoctocogene roxaparvovec, which has the potential to provide a treatment choice that addresses many of the unmet needs in hemophilia."

"We are optimistic that ABR may be maintained acceptably low through years three, four, and five after treatment with valoctocogene roxaparvovec in the GENEr8-1 study given the predictable, and not sudden or dramatic, change in Factor VIII expression in the later years following treatment in the Phase 1/2 study," said Hank Fuchs, M.D., President, Worldwide Research and Development at BioMarin. "The data show excellent hemostatic efficacy in the 6e13 and 4e13 vg/kg dose cohorts, which is maintained into year five and four, respectively. We look forward to sharing topline two-year data from all participants in the pivotal Phase 3 GENEr8-1 study in early 2022."

Safety Summary

Overall, the safety profile of valoctocogene roxaparvovec in the Phase 1/2 study remains consistent with previously reported data with no delayed-onset treatment related adverse events. All participants continue to remain off corticosteroids since the first year. No participants developed inhibitors to Factor VIII, and no participants withdrew from the study. No participants have developed thrombotic events. The most common adverse events associated with valoctocogene roxaparvovec occurred early after a single infusion and included short-lived infusion-associated reactions and transient, asymptomatic, and mild to moderate rise in the levels of certain proteins and enzymes measured in liver function tests with no long-lasting clinical sequelae.

Regulatory Status

The European Medicines Agency (EMA) validated BioMarin's resubmission of a Marketing Authorization Application (MAA) on July 15, 2021. In May 2021, the EMA granted the Company's request for accelerated assessment. Accelerated assessment potentially

reduces the time frame for the EMA Committee for Medicinal Products for Human Use (CHMP) and Committee for Advanced Therapies (CAT) to review a MAA for an Advanced Therapy Medicinal Product (ATMP), although an application initially designated for accelerated assessment can revert to the standard procedure during the review for a variety of reasons. The decision to grant accelerated assessment has no impact on the eventual CHMP and CAT opinion on whether a marketing authorization should be granted. A CHMP and CAT opinion is anticipated in the first half of 2022.

The MAA submission includes safety and efficacy data from the 134 subjects enrolled in the Phase 3 GENEr8-1 study, all of whom have been followed for at least one year after treatment with valoctocogene roxaparvovec, as well as four and three 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.

In the United States, BioMarin intends to submit two-year follow-up safety and efficacy data on all study participants from the Phase 3 GENEr8-1 study to support the benefit/risk assessment of valoctocogene roxaparvovec, as previously requested by the Food and Drug Administration (FDA). BioMarin is targeting a Biologics License Application (BLA) resubmission in the second quarter of 2022, assuming favorable study results, followed by an expected six-month review 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.

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 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 severe 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.

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 45 to 50% 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 adults 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 ISTH

Founded in 1969, the ISTH is the leading worldwide not-for-profit organization dedicated to advancing the understanding, prevention, diagnosis and treatment of thrombotic and bleeding disorders. The ISTH is an international professional membership organization with more than 7,700 clinicians, researchers and educators working together to improve the lives of patients in more than 110 countries around the world. Among its highly regarded activities and initiatives are education and standardization programs, research activities, meetings and congresses, peer-reviewed publications, expert committees and World Thrombosis Day on 13 October.

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 Statements

This press release contains forward-looking statements about the business prospects of BioMarin Pharmaceutical Inc., including without limitation, statements about: (i) the development of BioMarin's valoctocogene roxaparvovec program generally, (ii) the impact and potential of valoctocogene roxaparvovec gene therapy for treating patients with severe hemophilia A, (iii) plans to submit two-year follow-up safety and efficacy data on all study participants from the GENEr8-1 study in response to FDA's request for these data to support their benefit-risk assessment of valoctocogene roxaparvovec, (iv) our target Biologics License Application (BLA) submission date in the second quarter of 2022 assuming favorable study results, followed by an expected six-month review procedure by the FDA, (v) the potential approval and commercialization of valoctocogene roxaparvovec for the treatment of severe hemophilia A, including timing of such approval decisions, and (vi) sharing topline two-year data from all participants in the pivotal Phase 3 GENEr8-1 study in early 2022.

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 FDA, the European Commission and other regulatory authorities, including the potential impact of the COVID-19 pandemic on the regulatory authorities' abilities to issue such decisions and the timing of such decisions; the content and timing of decisions by local and central ethics committees regarding the clinical trials; BioMarin's ability to successfully manufacture valoctocogene roxaparvovec for the clinical trials and commercially, if approved; 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 March 31,

2021, 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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