BioMarin Announces Oral Presentation of Positive One-Year Results from Phase 3 Pivotal Trial with Valoctocogene Roxaparvovec Gene Therapy in Adults with Severe Hemophilia A at International Society on Thrombosis and Haemostasis (ISTH) 2021 Virtual Congress

Largest Gene Therapy Study in Hemophilia A Demonstrates Superiority in Key Clinical Efficacy Endpoints Compared to Baseline Factor VIII Prophylactic Therapy

Significantly Reduced Mean Annualized Bleeding Rate (ABR) by 84% (p-value <0.001) and mean annualized Factor VIII Utilization Rate by 99% (p-value <0.001) Compared to Baseline Factor VIII Prophylactic Therapy

SAN RAFAEL, Calif., July 19, 2021 /PRNewswire/ -- BioMarin Pharmaceutical Inc. (NASDAQ: BMRN) today announced new data for valoctocogene roxaparvovec, an investigational gene therapy for the treatment of adults with severe hemophilia A, in its positive pivotal study, GENEr8-1, during an oral presentation at the International Society on Thrombosis and Haemostasis (ISTH) 2021 Virtual Congress. The pivotal study demonstrated superiority to Factor VIII prophylaxis in key clinical efficacy endpoints. With 134 participants, this is the largest global Phase 3 study to date for gene therapy in hemophilia. All participants in the study received a single dose of valoctocogene roxaparvovec and completed a year or more of follow-up. Top-line one-year results from this study were previously communicated in January 2021.

New data presented at ISTH include more details on annualized bleeding rate (ABR) in all study participants and annualized Factor VIII utilization rate, in terms of international units per kilogram per year (IU/kg/year) of replacement Factor VIII. Over 90 percent (N=134) of all participants in the GENEr8-1 study had an annualized bleed rate (ABR) of zero or a lower bleed rate than baseline after week 4 after treatment with valoctocogene roxaparvovec.

New data presented at ISTH also include information on Factor VIII utilization after treatment with valoctocogene roxaparvovec. Mean annualized Factor VIII utilization rate, among a pre-specified group of prior participants in a non-interventional baseline observational study (rollover population; N=112) decreased from baseline on Factor VIII prophylaxis by 99% from 3961.2 (median 3754.4) to 56.9 (median 0) IU/kg/year after week 4 after treatment with valoctocogene roxaparvovec (p-value <0.001).

As previously shared in January 2021, data from the pre-specified rollover

population (N=112) in the GENEr8-1 study with a mean follow-up of 71.6 weeks demonstrated that in the pre-specified primary analysis for ABR, calculated through each subject's last assessment, a single dose of valoctocogene roxaparvovec significantly reduced mean ABR by 84% from a prospectively collected 4.8 (median 2.8) at baseline to 0.8 (median 0.0) bleeding episodes per year (p-value <0.001).

In addition, the mean annualized Factor VIII infusion rate was reduced by 99% from 135.9 (median 128.6) to 2.0 (median 0.0) infusions per year (p-value <0.001).

Table 1: Mean/Median Annualized Bleeding Rate (ABR) and FVIII Infusion Rate in Phase 3 GENEr8-1 Study Rollover Population (N=112) after Week 4 Through Week 52 at November 2020 Cut Off

	Phase 3 Rollover Population* On Factor VIII prophylaxis, before valoctocogene roxaparvovec infusion N=112	**Phase 3 Rollover Population* After valoctocogene roxaparvovec infusion N=112**
	Mean (SD) Median (IQR)	**Mean (SD) Median (IQR)**
Annualized Bleeding Rate (bleeding episodes per year)	4.8 (6.5) 2.8 (0.0, 7.6)	0.8 (3.0) 0.0 (0.0, 0.0)
Annualized FVIII Utilization Rate (IU per kg per year)	3961.2 (1751.5) 3754.4 (2799.5, 4706.8)	56.9 (194.6) 0.0 (0.0, 22.1)
Annualized FVIII Infusion Rate (infusions per year)	135.9 (52.0) 128.6 (104.1, 159.9)	2.0 (6.4) 0.0 (0.0, 0.9)

**See study description for patient population information.*

Study participants also experienced a clinically meaningful increase in endogenous Factor VIII expression. At the end of the first year post-infusion with valoctocogene roxaparvovec, participants in the modified intent-to-treat (mITT) population (N=132) had a significant increase in mean endogenous Factor VIII expression level from an imputed baseline of 1 IU/dL to 42.9 IU/dL (median 23.9) (p-value <0.001) as measured by the chromogenic substrate (CS) assay, supporting the marked clinical benefits observed with abrogation of bleeding episodes and Factor VIII utilization and infusion rates. In a subset of the mITT population that had been dosed at least two years prior to the data cut date (N=17), 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.

Table 2: Factor VIII Activity Levels in 12-Month Intervals

Median Factor VIII Activity, IU/dL	**Phase 3 mITT Population* (N=132) Mean (SD) Median**	**Phase 3 mITT Subset Population** (N=17) Mean (SD) Median**
Week 52	42.9 (45.5) 23.9 (11.9, 62.3)	42.2 (50.9) 23.9 (11.2, 55.0
Week 104	N/A	24.4 (29.2) 14.7 (6.4, 28.6)

** mITT = modified intent-to-treat population, which excludes 2 HIV- positive subjects dosed 2 or more years prior to November 2020 data cut.*

***Includes only HIV-negative subjects dosed 2 or more years prior to Nov 2020 data cut date. One participant was lost to follow-up at 66.1 weeks and was henceforth imputed to have a Factor VIII activity of 0 IU/dL through 104 weeks.*

"The demonstrated bleed control at 52 weeks and beyond in this pivotal study supports our thesis that gene therapy can play an important role in the treatment of severe hemophilia A and potentially creates the possibility for a new treatment paradigm," said Margareth C. Ozelo, MD, PhD, Director, INCT do Sangue Hemocentro UNICAMP, University of Campinas and Lead Principal Investigator of the GENEr8-1 Study. "It is encouraging to see meaningful endogenous Factor VIII expression and decreases in bleeding and Factor VIII infusions for people in this study. These pivotal results contribute to the growing

body of data to increase understanding of the safety and efficacy of gene therapy treatment over time."

"From the start of our valoctocogene roxaparvovec program, our goal remains to advance treatment options for people with severe hemophilia A in light of the unmet need in bleed control. Current prophylactic therapies for hemophilia A cannot maintain Factor VIII levels for sustained periods, leading to the need for frequent, regular infusions or injections while still having a risk of ongoing, unpredictable bleeds and unavoidable, irreversible joint damage even with standard of care treatment," said Hank Fuchs, M.D., President of Worldwide Research and Development at BioMarin. "These data build upon the foundation for a potential transformative treatment option that addresses the root cause of severe hemophilia A. Later at ISTH, we look forward to sharing five years of clinical data from the ongoing Phase 1/2 study with the longest duration of clinical experience, which complements this pivotal Phase 3 study, the largest study of a gene therapy in hemophilia A."

Valoctocogene Roxaparvovec Safety

Overall, in the Phase 3 study, valoctocogene roxaparvovec has been well tolerated by the 134 participants who received a single 6e13 vg/kg dose. No participants withdrew due to adverse events. No participants developed inhibitors to Factor VIII, or experienced thromboembolic events. One participant was lost to follow-up. Infusion reactions were defined as any AEs occurring within 48 hours post-infusion. The most common infusion reactions were nausea (14.2%), fatigue (7.5%), and headache (6.0%). Systemic hypersensitivity during or following infusion was mitigated by slowing or pausing infusion and treating with supportive medications, as indicated. All four (3.0%) participants with an interruption due to infusion-related symptoms were able to complete their infusion. Twenty-two (16.4%) participants experienced a total of 43 serious adverse events (SAEs), and all SAEs resolved.

Common, steroid-related side effects can occur with temporary use of corticosteroid (or alternative immunosuppressants) to manage ALT elevation. ALT elevation was the most common AE. Overall, 79% of participants received corticosteroids per protocol as treatment for ALT elevation. The average duration of corticosteroid treatment was 33 weeks. Overall, 72% of participants who used any corticosteroids reported AEs attributed to their use, most commonly acne, insomnia, cushingoid changes, and weight increased. Three participants reported SAEs attributed to corticosteroids. Other immunosuppressants were used by 29% of participants for ALT elevation due to contraindication, side effects, or poor or no response to corticosteroid treatment. No

Grade 4 ALT elevations occurred, and no participants met Hy's law criteria for drug-induced liver injury.

GENEr8-1 Study Description

The global Phase 3 GENEr8-1 study evaluates superiority of valoctocogene roxaparvovec at the 6e13 vg/kg dose compared to FVIII prophylactic therapy. All study participants had severe hemophilia A at baseline, defined as less than or equal to 1 IU/dL of Factor VIII activity. The study included 134 total participants, all of whom had a minimum of 12 months of follow-up at the time of the data cut. The first 22 participants were directly enrolled into the Phase 3 study, 17 of whom were HIV-negative and dosed at least 2 years prior to the data cut date (referred to as the subset). The remaining 112 participants (rollover population) completed at least six months in a separate non-interventional study to prospectively assess bleeding episodes, Factor VIII use, and health-related quality of life while receiving Factor VIII prophylaxis prior to rolling over to receive a single infusion of valoctocogene roxaparvovec in the GENEr8-1 study.

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 hemophilia A. The Company is also running a Phase 1/2 Study with the 6e13 vg/kg dose of valoctocogene roxaparvovec in people with hemophilia A 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 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 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 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 anticipated timing of a CHMP and CAT opinion in the first half of 2022, (iii) BioMarin's intention to submit to the U.S. Food and Drug Administration (FDA) 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, (iv) BioMarin targeting resubmission of a Biologics License Application in the second quarter of 2022 assuming favorable study results, followed by an expected six-month review procedure by the FDA, (v) the anticipated Phase 1/2 study to be presented later at ISTH and (vi) the timing of the regulatory activities in the U.S and Europe, including validation and timing of potential approvals and the expected review procedures. 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 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 decisionsby local and central ethics committees regarding the clinical trials; our 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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