BioMarin Announces Stable and Durable Annualized Bleed Control for ROCTAVIAN™ in Largest Phase 3 Gene Therapy Study in Adults with Severe Hemophilia A; 134-Participant Study Met All Primary and Secondary Efficacy Endpoints at 3-Year Analysis

- Mean Annualized Bleed Rate Reduced by 80% from Baseline and Factor VIII Usage Reduced by 94% in Year 3 Compared to Baseline

- 92% of Patients off Prophylaxis at the End of Year 3

- First Outcomes-Based Agreement (OBA) Recently Signed in Germany; Additional Agreements Expected to be Signed in Coming Weeks

- U.S. Food and Drug Administration Pre-License Inspection of Manufacturing Facility Complete

SAN RAFAEL, Calif., Jan. 8, 2023 /PRNewswire/ -- BioMarin Pharmaceutical Inc. (NASDAQ: BMRN), a global biotechnology company dedicated to transforming lives through genetic discovery, today announced positive results from more than three years of follow up from its ongoing global Phase 3 GENEr8-1 study of ROCTAVIAN™ (valoctocogene roxaparvovec), an investigational one-time gene therapy for the treatment of adults with severe hemophilia A. This is the largest and longest global Phase 3 study to date for any gene therapy in hemophilia with 134 participants.

The ROCTAVIAN data are summarized in the following table:

		Phase 3 (6e13 vg/kg dose)	
		In Year 3*	In Year 4**
FVIII Activity (chromogenic)	Mean	18.8	15.2
	Median	8.4	7.4
Annualized Bleeding Rate*** (bleeding	Mean	1.0	0.8

episodes per year)	Median	0.0	0.0
Annualized FVIII Utilization (infusions per year)	Mean	8.4	11.1
	Median	0.0	0.0

**N=132 (FVIII Activity); N=112 (ABR and AFR). Two of these patients discontinued from the study prior to reaching Year 3. FVIII imputed to be 0 IU/dL; no imputation was carried out for ABR and AFR.*
***N=17. One of these patients discontinued from the study prior to reaching Year 4. FVIII activity imputed to be 0 IU/dL; no imputation was carried out for ABR and AFR.*
****Annualized rate is for treated bleeds.*

P values for all primary and secondary endpoint comparisons were <0.001 and include the entire treatment period.

In response to the U.S. Food and Drug Administration (FDA)'s request, and consistent with the FDA's guidance for other gene therapy trials for hemophilia, BioMarin has also analyzed annualized bleeding rate for all bleeds, regardless of whether those bleeds were treated with exogenous Factor VIII replacement. Results from that analysis were similar to those reflected in the table above. In Year 3, the mean/median ABR for all bleeds was 1.4/0.0, and in Year 4 the mean/median ABR for all bleeds was 1.6/1.0.

At the end of Year 3, 92% of patients remained off prophylaxis. Those patients who returned to Factor VIII or emicizumab prophylaxis did so safely.

"We continue to learn more about the durability, safety and efficacy of valoctocogene roxaparvovec," said Steven Pipe, M.D., Professor of Pediatrics and Pathology at the University of Michigan and an investigator in the Phase 3 study. "I am encouraged to see the consistent clinical response and the significant number of study participants who remain off prophylaxis after three years. This shows the potential transformative impact of this single treatment event for people with severe hemophilia A."

BioMarin plans to present additional data from this study at upcoming medical meetings.

"The three-year data reinforce our belief that ROCTAVIAN has the potential to

fundamentally transform the treatment of severe hemophilia A for patients and eliminate the burden of prophylaxis," said Hank Fuchs, M.D., President of Worldwide Research and Development at BioMarin. "We look forward to sharing these data with the FDA as part of our ongoing regulatory review. We remain grateful to the bleeding disorders community for its support of our robust clinical program."

Commercial Progress in Europe

As the company has previously indicated, BioMarin is targeting outcomes-based agreements (OBAs) with the three largest health insurance groups that represent about 80% of German lives. The company has executed an OBA with one of the three. The company expects to sign additional agreements in the coming weeks in Germany and continues to progress the European launch of ROCTAVIAN on a country-by-country basis, including meetings with authorities in France and the submission of the reimbursement dossier in Italy.

For covered patients, the agreements provide for companion diagnostic testing and reimbursement of ROCTAVIAN, allowing physicians to prescribe and patients to be treated with therapy.

The OBAs in Germany are multiyear agreements that cover payer risk of patients potentially returning to prophylaxis through direct BioMarin financial commitment in return for substantial and full upfront payment.

"We continue to see a high level of interest from physicians in Germany. Treatment centers are ready to go, and our market research indicates that there are approximately 40 patients queued up for pre-treatment screening," said Jeff Ajer, Executive Vice President and Chief Commercial Officer of BioMarin. "We are pleased that these outcomes-based agreements will enable access for individuals with severe hemophilia A."

Valoctocogene Roxaparvovec Safety

Overall, to date, a single 6e13 vg/kg dose of valoctocogene roxaparvovec has been well tolerated with no delayed-onset treatment related adverse events (AEs). In Year 3, no new treatment-related serious adverse events or Grade 3 events attributed to valoctocogene roxaparvovec or corticosteroid use emerged.

The most common AEs associated with valoctocogene roxaparvovec have occurred early and included transient infusion associated reactions and mild to moderate rise in liver enzymes with no long-lasting clinical sequelae. Alanine aminotransferase (ALT) elevation,

a laboratory test of liver function, has remained the most common adverse drug reaction. Other adverse reactions have included aspartate aminotransferase (AST) elevation (101 participants, 63%), nausea (55 participants, 34%), headache (54 participants, 34%), and fatigue (44 participants, 28%). No participants have developed inhibitors to Factor VIII, thromboembolic events or malignancy associated with valoctocogene roxaparvovec.

Regulatory Status

These data will be shared with the FDA as part of the agency's ongoing review of the Biologics License Application (BLA) of ROCTAVIAN. The PDUFA date is March 31, 2023, subject to possible agency extension.

Additionally, the FDA completed a Pre-License Inspection of the manufacturing facility in early December. BioMarin has provided responses to the comments and observations received at the close of the inspection, and the company believes all are addressable.

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 expected to address an unmet medical need in patients with serious conditions. The RMAT designation is complementary to Breakthrough Therapy Designation, which the company received for valoctocogene roxaparvovec in 2017.

In addition to the RMAT Designation and Breakthrough Therapy Designation, BioMarin's valoctocogene roxaparvovec also received orphan drug designation from the European Medicines Agency (EMA) and FDA for the treatment of severe hemophilia A. Orphan drug designation is reserved for medicines treating rare, life-threatening, or chronically debilitating diseases. The European Commission (EC) granted conditional marketing authorization to valoctocogene roxaparvovec gene therapy under the brand name ROCTAVIAN on August 24, 2022.

GENEr8-1 Study Description

The global Phase 3 GENEr8-1 study evaluates superiority of valoctocogene roxaparvovec at the 6e13 vg/kg dose compared to the current standard of care, 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 36 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 48 months or 4 years prior to the data cut date. 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.

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 also conducting a Phase 3, 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 (Study 270-303). Also ongoing is a Phase 1/2 Study with the 6e13 vg/kg dose of valoctocogene roxaparvovec in people with severe hemophilia A with pre-existing AAV5 antibodies (Study 270-203) and a Phase 1/2 Study with the 6e13 vg/kg dose of valoctocogene roxaparvovec in people with severe hemophilia A with active or prior Factor VIII inhibitors (Study 270-205).

About Hemophilia A

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.

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 (Factor VIII 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% of the hemophilia A population. People with hemophilia A with moderate (Factor VIII 1-5%) or mild (Factor VIII 5-40%) disease show a much-reduced propensity to bleed. Individuals with severe hemophilia A are treated with a prophylactic regimen of intravenous Factor VIII infusions administered 2-3 times per week (100-150 infusions per year) or a bispecific monoclonal antibody that mimics the activity of Factor VIII administered 1-4 times per month (12-48 injections or shots 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.

About BioMarin

Founded in 1997, BioMarin is a global biotechnology company dedicated to transforming lives through genetic discovery. The company develops and commercializes targeted therapies that address the root cause of the genetic conditions. BioMarin's unparalleled research and development capabilities have resulted in eight transformational commercial therapies for patients with rare genetic disorders. The company's distinctive approach to drug discovery has produced a diverse pipeline of commercial, clinical, and pre-clinical candidates that address a significant unmet medical need, have well-understood biology, and provide an opportunity to be first-to-market or offer a substantial benefit over existing treatment options. For additional information, please visit www.biomarin.com.

Forward-Looking Statements

This press release contains forward-looking statements about the business prospects of BioMarin Pharmaceutical Inc. (BioMarin), including without limitation, statements about: the development of BioMarin's ROCTAVIAN™ (valoctocogene roxaparvovec) program generally, and the Phase 3 study results particularly; the potential for ROCTAVIAN to fundamentally transform the treatment of severe hemophilia A for patients and eliminate the burden of prophylaxis; BioMarin's plans to share data from the Phase 3 study of ROCTAVIAN with the FDA as part of the agency's ongoing regulatory review of BioMarin's Biologics License Application for ROCTAVIAN; BioMarin plans to present additional data from the Phase 3 study of ROCTAVIAN at upcoming medical meetings; BioMarin's plans to target the remaining two largest health insurance groups in Germany, and BioMarin's expectation to sign additional outcomes-based agreements (OBAs) providing for companion diagnostic testing and reimbursement of ROCTAVIAN with German health insurance groups in the coming weeks; the number of patients in Germany queued up for pre-treatment screening for ROCTAVIAN; the expectation that OBAs for ROCTAVIAN will enable access for individuals with severe hemophilia; BioMarin's continued progress of the European launch of ROCTAVIAN on a country-by-country basis, including BioMarin's plans to hold meetings with authorities in France and the submission of the reimbursement dossier in Italy; the timing of the PDUFA target action date and the potential for the FDA to extend such date; and BioMarin's belief that all comments and observations from the FDA's Pre-License Inspection of the ROCTAVIAN manufacturing facility are addressable. 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 ROCTAVIAN, 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 decisions by local and central ethics committees regarding the clinical trials; BioMarin's ability to successfully manufacture ROCTAVIAN for clinical trials and commercial sales; BioMarin's ability to enter into OBAs with insurance groups in Germany; and those factors detailed in BioMarin's filings with the Securities and Exchange Commission (SEC), including, without limitation, the factors contained under the caption "Risk Factors" in BioMarin's Quarterly Report on Form 10-Q for the quarter ended September 30, 2022 as such factors may be updated by any subsequent reports. Stockholders are urged not to place undue reliance on forward-looking statements, which speak only as of the date hereof. BioMarin is under no obligation, and expressly disclaims any obligation to update or alter any forward-looking statement, whether as a result of new information, future events or otherwise.

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