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

- Annualized Bleeding Rate (ABR) Reduced by 85% from Baseline, Demonstrating Superiority to Factor VIII Prophylaxis

- Mean Factor VIII Activity of 23 IU/dL (Chromogenic Assay); 36 IU/dL (One-Stage Assay) Observed at Year 2

- Company Plans to Present Additional Data at Upcoming Medical Meetings

- Marketing Authorization Application under review with the European Medicines Agency (EMA) and Regulatory Submission to FDA Expected in 2Q 2022

- Conference Call and Webinar to be Held Today, Sunday, January 9, 2022 at 5:00 PM Eastern Time

SAN RAFAEL, Calif., Jan. 9, 2022 /PRNewswire/ -- BioMarin Pharmaceutical Inc. (NASDAQ: BMRN) today announced positive results from its ongoing global Phase 3 GENEr8-1 study of valoctocogene roxaparvovec, an investigational gene therapy for the treatment of adults with severe hemophilia A. This is the largest global Phase 3 study to date for any gene therapy in hemophilia, with 134 participants.

In the GENEr8-1 Phase 3 study, Annualized Bleeding Rate (ABR) was significantly reduced by 4.1 treated bleeds per year (p-value <0.0001), or 85% from a baseline mean of 4.8 (median 2.8), in the pre-specified primary analysis in participants from a prior non-interventional study (rollover population; N=112; median follow-up of 110 weeks). The mean ABR was 0.8 (median 0.0) through the entire efficacy evaluation period, 0.9 (median 0.0) during year one, and 0.7 (median 0.0) during year two.

Valoctocogene roxaparvovec also significantly reduced the mean annualized Factor VIII infusion rate in the rollover population by 133 infusions per year (p-value <0.0001) or 98% from baseline. The mean annualized infusion rate was 2.6 (median 0.0) through the entire efficacy evaluation period, 1.5 (median 0.0) during year one, and 3.4 (median 0.0) during year two.

At the end of the second year post-infusion with valoctocogene roxaparvovec, participants in the modified intent-to-treat (mITT) population (N=132) had a mean endogenous Factor VIII activity level of 23.0 (median 11.8) IU/dL, as measured by the chromogenic substrate (CS) assay and 36.1 (median 21.6) IU/dL, as measured by the one-stage (OS) assay.

In a subset of the mITT population that had been dosed at least three years prior to the data cut (N=17), mean Factor VIII activity was 16.8 (median 9.3) IU/dL by CS assay and 27.0 (median 19.1) IU/dL by OS assay at the end of year three. The mean cumulative ABR for this subpopulation was 0.7 (median 0.0) through the entire efficacy evaluation period (median follow up 174 weeks) and 0.6 (median 0.0) during year three.

For comparison, the table below provides results from both the Phase 3 GENEr8-1 Study and the Phase 1/2 Study (201), by Study Year, for Factor VIII activity (by CS assay), ABR, and annualized Factor VIII utilization (infusions per year).

Two-Year Results Demonstrate Consistent Clinical Benefit in ABR and Factor VIII Utilization Across Phase 3 and Phase 1/2 Studies with Valoctocogene Roxaparvovec

		Phase 3			**Phase 1/2**				**Phase 1/2**				
		6e13 vg/kg dose			**4e13 vg/kg cohort, N=6**				**6e13 vg/kg cohort, N=7***				
		Year 1 N = 132/112**	**Year 2 N= 132/112****	**Year 3 N=17*****	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Ye**
FVIII Activity (Chromogenic)	**Mean**	42.8	23	16.8	21.1	12.3	10.2	5.6	63.6	36.1	29.9	19	1
	Median	23.9	11.8	9.3	23.8	11.6	7.3	4.8	60.3	26.2	17.1	14.5	8
Annualized Bleeding Rate (bleeding episodes per year)	**Mean**	0.9	0.7	0.6	0.9	1.2	0.5	1.7	1.3	0.2	0.7	1.3	(
	Median	0	0	0	0	0	0	1	0	0	0	0	
Annualized FVIII Utilization (infusions per year)	**Mean**	1.5	3.4	(this metric not part of N=17	1.6	6.8	8.6	7.8	1.8	8.8	5.5	4.6	5
	Median	0	0		0	0.5	1.5	3	0	0	0	0.5	

				analysis)									

**N=6 for Annualized Bleeding Rate and Annualized FVIII Utilization as one on-demand patient was excluded*

*** mITT population (N=132) for FVIII Activity endpoint; Rollover Population (N=112) for Annualized Bleeding Rate and Annualized FVIII Utilization endpoints*

**** mITT subset population dosed ≥ 3 years prior to data cut*

Evaluation period begins at whichever occurred later, 5 weeks post-infusion or 3 days after the end of routine FVIII prophylaxis; values differ slightly from those reported previously using the LOCF imputation method for missing data as the statistical analysis plan was updated to use a more conservative method based on FDA feedback; corresponding changes were also made to the study 201 results to facilitate comparison.

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

"A potential single treatment that provides a durable response for years could be a game-changer by offering a transformative treatment choice beyond existing therapies and addressing an unmet medical need for people with hemophilia A," said Steven W. Pipe, MD, Professor of Pediatrics and Pathology at the University of Michigan and investigator in the Phase 3 study. "As a principal investigator, I have witnessed the transformative liberating potential of valoctocogene roxaparvovec for hemophilia A in my own clinical trial participants. I'm delighted to see these results broadly confirmed in the largest study of its kind."

"We are delighted that our perseverance on behalf of people with hemophilia A has led to today's transformative results in the largest gene therapy study for hemophilia A," said Hank Fuchs, M.D., President of Worldwide Research and Development at BioMarin. "We are grateful for the support of the bleeding disorders community to conduct this clinical program. These results show that valoctocogene roxaparvovec could profoundly change the way hemophilia A is treated. We are looking forward to continuing to work with health authorities to bring this therapy to patients with hemophilia A."

Valoctocogene Roxaparvovec Safety

Overall, in the Phase 3 study, valoctocogene roxaparvovec has continued to be well tolerated. All participants received a single 6e13 vg/kg dose. No participants developed inhibitors to Factor VIII, malignancy, or thromboembolic events. During year two, no new safety signals emerged, and no treatment-related serious adverse events (SAE) were reported. Most patients had discontinued any corticosteroid (CS) use in year one, and there were no CS-related SAEs in the remaining patients being tapered off CS in year two. Overall, the most common adverse events (AE) associated with valoctocogene roxaparvovec 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 (119 participants, 89%), a laboratory test of liver function, remained the most common AE. Other common adverse events were headache (55 participants, 41%), arthralgia (53 participants, 40%), nausea (51 participants, 38%), aspartate aminotransferase (AST) elevation (47 participants, 35%), and fatigue (40 participants, 30%).

Regulatory Status

The European Medicines Agency (EMA) validated BioMarin's resubmission of a Marketing Authorization Application (MAA) and a Committee for Medicinal Products for Human Use (CHMP) and Committee for Advanced Therapies (CAT) opinion is anticipated in the first half of 2022.

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). Based on these results, BioMarin is planning to meet with FDA to discuss the resubmission of a Biologics License Application (BLA) targeted for the second quarter of 2022, followed by an expected six-month review by the FDA.

Valoctocogene roxaparvovec has received both Regenerative Medicine Advanced Therapy (RMAT) designation and Breakthrough Therapy Designation from FDA, which are intended to expedite development of drugs for serious or life-threatening diseases and conditions. In addition to the RMAT Designation and Breakthrough Therapy Designation, valoctocogene roxaparvovec also has received Orphan Drug Designation from the FDA and EMA for the treatment of severe hemophilia A.

Conference Call and Webinar to be Held Today at 5:00 PM Eastern Time

Join from a PC, Mac, iPad, iPhone or Android device:

Please click here to join live Zoom webinar at 5pm Eastern Time.

Or to join by phone, dial (for higher quality, dial a number based on your current location):

US: +1 669 900 6833 or +1 346 248 7799 or +1 253 215 8782 or +1 301 715 8592 or +1 312 626 6799 or +1 929 205 6099

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International numbers available here.

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 24 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 36 months or 3 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.

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 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 Statements

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, and the Phase 3 results particularly; the impact of valoctocogene roxaparvovec gene therapy for treating patients with severe hemophilia A, the potential for valoctocogene roxaparvovec to reduce or eliminate bleeds, reduce the number of Factor VIII infusions, the predictive value of the Phase 1/2 study, and the ongoing clinical programs generally. 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 decisions by local and central ethics committees regarding the clinical trials; our ability to successfully manufacture valoctocogene roxaparvovec; 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 Annual and quarterly Reports on Forms 10-K and 10-Q, 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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