BioMarin Provides 3 Years of Clinical Data from Ongoing Phase 1/2 Study of Valoctocogene Roxaparvovec Gene Therapy for Severe Hemophilia A

Substantial Reduction in excess of 92% in Mean Bleed Rate Requiring Factor VIII Infusions; Sustained over the Period of Observation (3 Years in High Dose and 2 Years in Low Dose)
Rate of FVIII Change Continued to be Expression Level Dependent, Slowed in Year 3, and Appears to be Approaching Plateau
Conference Call and Webcast to be Held Tuesday, May 28, 2019 at 8:00 AM Eastern

SAN RAFAEL, Calif., May 28, 2019 /PRNewswire/ -- BioMarin Pharmaceutical Inc. (NASDAQ: BMRN) announced today an update to its previously reported results of an open-label Phase 1/2 study of valoctocogene roxaparvovec, an investigational gene therapy treatment for adults with severe hemophilia A. The three-year update demonstrated that bleed rate control with valoctocogene roxaparvovec 6e13 vg/kg dose was maintained for a third year with a median Annualized Bleed Rate (ABR) of 0 and mean ABR of 0.7 in that year. In addition, Factor VIII levels in the 6e13 vg/kg dose appeared to be approaching a plateau in year three. Factor VIII levels measured with the chromogenic substrate (CS) assay at the end of year three were mean and median of 32.7 IU/dL and 19.9 IU/dl, respectively, compared with mean and median of 36.4 IU/dL and 26.2 IU/dL, respectively, at the end of year two. The full updated results will be submitted for presentation at the International Society on Thrombosis and Haemostasis 2019.

"These data confirm that valoctocogene roxaparvovec has the potential to profoundly impact the lives of people with severe hemophilia A through a sustained reduction in bleeds and factor VIII usage," said Hank Fuchs, M.D., President, Global Research and Development at BioMarin. "Importantly, we've now observed that maintenance of factor expression is a function of expression level and time. Therefore, by three years post a one-time infusion of valoctocogene roxaparvovec, we anticipate we are nearing the plateau of expression. More conservative statistical modeling anticipates that bleeding control will be maintained for at least eight years after gene transfer. This is fantastic news for the hemophilia community."

"With three years of data, it's clear that valoctocogene roxaparvovec has the potential to change the way we treat this debilitating disease, which can improve the quality of life for people with severe hemophilia A," said John Pasi, M.B., Ch.B., Ph.D., from Barts and the London School of Medicine and Dentistry and primary investigator for this Phase 1/2 study. "For people who have had to inject themselves with factor VIII every other day to prevent bleeding, this treatment has the potential to be transformational."

Annualized Bleed Rate and Factor VIII Use in 6e13 vg/kg Cohort

In the 6e13 vg/kg cohort, the data showed substantial and sustained reductions in bleeding that required Factor VIII infusions. In the year prior to study entry, the mean ABR was 16.3 and the median was 16.5. After three years, the ABR was a mean of 0.7 and a median of zero. This represents a 96% reduction in mean (ABR) over three years, with continued absence of target joints and target joint bleeds during the three years observed. In the first, second and third years, 71%, 86% and 86%, respectively, of study participants had zero bleeds requiring Factor VIII infusions compared to 14% who had zero bleeds requiring Factor VIII infusions in the year prior to study entry. There was a 96% reduction in mean FVIII usage over three years. In the first, second and third years, there was a 98%, 94%, and 96% reduction in mean FVIII usage, respectively.

Valoctocogene Roxaparvovec Reduces Bleeds and Factor VIII Use: Summary of Annualized Bleeding Rate (ABR) and FVIII Usage of 6e13 vg/kg Dose Patients Previously on Prophylaxis (N=6)* at April 1, 2019 data cut

6e13 vg/kg Dose	**Before valoctocogene roxaparvovec Infusion*** **	**After valoctocogene roxaparvovec Infusion**** during Year 1**	**After valoctocogene roxaparvovec Infusion**** during Year 2**	**After valoctocogene roxaparvovec Infusion**** during Year 3**
	Median (mean, SD)	**Median (mean, SD)**	**Median (mean, SD)**	**Median (mean, SD)**
Annualized Bleeding Rate (bleeding episodes per year per subject)**	16.5 (16.3, 15.7)	0.0 (0.9, 2.2)	0.0 (0.2, 0.4)	0.0 (0.7, 1.6)
Annualized FVIII Infusions (infusions per year per subject)**	138.5 (136.7, 22.4)	0.0 (2.1, 5.3)	0.0 (8.8, 21.0)	0.0 (5.5, 9.4)

**A 7th patient received Factor VIII on demand prior to treatment with BMN 270 and was not included in analysis.*

***Post infusion data were based on data after Week 4*
****Obtained from medical records.*
*****5 of 6 participants had 0 bleeds requiring Factor VIII infusions and 4 of 6 participants had 0 Factor VIII infusions after Week 4.*

Annualized Bleed Rate and Factor VIII Use in 4e13 vg/kg Cohort

In the 4e13 vg/kg cohort, the data showed substantial and sustained reductions in bleeding requiring Factor VIII infusions. In the year prior to study entry, the mean Annualized Bleed Rate (ABR) was 12.2 and the median was 8. After two years, the ABR was a mean of 1.2 and a median of zero. This represents a 92% reduction in mean Annualized Bleed Rate (ABR). In the first and second years, 83% and 67%, respectively, of study participants had zero bleeds requiring Factor VIII infusions compared to 17% requiring Factor VIII infusions in the year prior to study entry. There was a 97% reduction in mean FVIII usage over two years. In the first, and second years, there was a 99% and 95% reduction in mean FVIII usage, respectively.

Valoctocogene Roxaparvovec Reduces Bleeds and Factor VIII Use: Summary of Annualized Bleeding Rate (ABR) and FVIII Use Rate of 4e13 vg/kg Dose for Patients Previously on Prophylaxis (N=6) at April 1, 2019 data cut

4e13 vg/kg Dose	Before valoctocogene roxaparvovec Infusion	After valoctocogene roxaparvovec Infusion during Year 1	After valoctocogene roxaparvovec Infusion during Year 2
	Median (mean, SD)	Median (mean, SD)	Median (mean, SD)
Annualized Bleeding Rate* **(bleeding episodes per year per subject)**	8.0 (12.2, 15.4)	0.0 (0.9, 2.2)	0.0 (1.2, 2.4)
Annualized FVIII Use Rate* **(infusions per year per subject)**	155.5 (146.5, 41.6)	0.0 (2.0, 4.3)	0.5 (6.8, 15.6)

**Post-infusion data were based on data after Week 4.*

Factor VIII Activity Levels for 6e13 vg/kg Cohort

For the 6e13 vg/kg cohort, mean Factor VIII activity levels over three years support reductions in bleed rates and show a flattening rate of decline in the chromogenic substrate (CS) and one-stage (OS) assays expressed as an international unit per deciliter (IU/dL). At the end of the first, second and third years, post-infusion, mean Factor VIII activity level of the 6e13 vg/kg cohort was 64.3, 36.4 and 32.7 IU/dL respectively as measured by the CS assay. The mean results of the OS assay at the end of the first, second and third year were 103.8, 59.0, and 52.3 IU/dL, respectively. The median Factor VIII activity levels at the end of the first, second and third years were 60.3, 26.2 and 19.9 ID/dL respectively as measured by the CS assay. The median results of the OS assay at the end of the first, second and third year were 88.6, 45.7, and 29.8 IU/dL, respectively. During the second and third year from receiving the infusion, factor VIII levels in the 6e13 vg/kg dose declined at the rate of 5.72 IU/dL per year based on the slope of the linear regression of all the factor VIII data from weeks 53 to week 156.

Mean and Median Factor VIII Activity Levels (IU/dL) of 6e13 vg/kg Dose Patient Visit at Year End (N=7) at April 1, 2019 Data Cut*

	Year 1**	Year 2**	Year 3**
Mean (Median) Factor VIII Activity Levels (IU/dL) as Measured using Chromogenic Substrate Assay	64.3 (60.3)	36.4 (26.2)	32.7 (19.9)
Mean (Median) Factor VIII Activity Levels (IU/dL) as Measured using One-Stage Assay	103.8 (88.6)	59.0 (45.7)	52.3 (29.8)

**All patients had severe hemophilia A at baseline, defined as less than or equal to 1 IU/dL of Factor VIII activity levels.*
***Weeks were windowed by +/- 2 weeks before 104 weeks, after 104 weeks, weeks were windowed by +/- 4 weeks, and for week 32, one patient did not have a Factor VIII activity level available.*

Factor VIII Activity Levels for 4e13 vg/kg Cohort

For the 4e13 vg/kg cohort, mean Factor VIII activity levels over two years support reductions in bleed rates and also show a flattening rate of decline in the one-stage (OS) and chromogenic substrate (CS) assays expressed as an international unit per deciliter (IU/dL). At the end of the first and second years, post-infusion, mean Factor VIII activity level of the 4e13 vg/kg cohort was 21.0 and 14.7 IU/dL respectively as measured by the CS assay. The mean results of the OS assay at the end of the first and second year was 31.4 and 23.2 IU/dL respectively. The median Factor VIII activity levels at the end of the first and second years were 22.9 and 13.1 IU/dL, respectively as measured by the CS

assay. The median results of the OS assay at the end of the first and second year was 31.7 and 23.5 IU/dL respectively. During the second year from receiving the infusion, factor VIII levels in the 4e13 vg/kg dose declined at the rate of 1.56 IU/dL per year based on the slope of the linear regression of all the factor VIII data from weeks 53 to 104.

Mean and Median Factor VIII Activity Levels (IU/dL) of 4e13 vg/kg Dose Patient Visit at Year End (N=7) at April 1, 2019 Data Cut*

	Year 1**	**Year 2****
Mean (Median) Factor VIII Activity Levels (IU/dL) as Measured using Chromogenic Substrate Assay	21.0 (22.9)	14.7 (13.1)
Mean (Median) Factor VIII Activity Levels (IU/dL) as Measured using One-Stage Assay	31.4 (31.7)	23.2 (23.5)

**All patients had severe hemophilia A at baseline, defined as less than or equal to 1 IU/dL of Factor VIII activity levels.*
***For analysis, weeks were windowed by +/- 2 weeks before 104 weeks and for week 32, one patient did not have a Factor VIII activity level available.*

Factor VIII Activity Level Changes Continued to be Expression Level Dependent, Slowed in Year Three, and Appears to be Approaching Plateau

The three years of data available suggest that a loss of factor VIII expression is dependent on the level of expression and appears to decline slower as time and expression level decline. At the current rates of decline, based on a statistical model of expression as a function of level and time to extrapolate hemostatic efficacy, it appears that the Factor VIII activity levels are approaching a plateau and project sustained Factor VIII expression for an extended period of time.

The estimates of durability of bleed control are based on a statistical model developed by the company to estimate the average time until factor levels approach 5 IU/dl. Extrapolation beyond week 156 assumes a continued decline at a rate equal to the estimated slope for the FVIII activity of the 6E13 vg/kg dose from >52 weeks to ≤ 156 weeks based on a linear regression (slope: -5.72 IU/year) until mean FVIII activity reaches that observed in the 4e13 vg/kg levels at Year 2. At that point, the model assumes the rate of decline based on the estimated slope for 4E13 vg/kg dose from > 52 weeks to ≤ 104 weeks based on a linear regression (slope -1.56 IU/year).

Conference Call and Webcast to be Held May 28, 2019 at 8:00 AM Eastern Time

Interested parties may access a live video webcast that will include audio and slides of the presentations via the investor section of the BioMarin website. A replay of the meeting will be archived on the site for one week.

For those who choose not to listen and view the event via webcast, dial-in information for the audio portion of the webcast can be accessed using:

U.S. / Canada Dial-in Number: (866) 502-9859
International Dial-in Number: (574) 990-1362
Conference ID: 2295086

Replay Dial-in Number: (855) 859-2056
Replay International Dial-in Number: (404) 537-3406
Conference ID: 2295086

Valoctocogene Roxaparvovec Safety

Overall, valoctocogene roxaparvovec continues to have a favorable safety profile and has been well-tolerated by participants across all doses, including the two participants who received the lowest doses of 6e12 and 2e13 vg/kg, respectively. No participants developed inhibitors to Factor VIII, and no participants withdrew from the study. The most common adverse events (AEs) across all dose cohorts were alanine aminotransferase (ALT) elevation (11 participants, 73%); arthralgia, (10 participants, 67%); aspartate aminotransferase elevation (8 participants, 53%); headache (7 participants, 47%); back pain, fatigue, and upper respiratory tract infection (6 participants, 40%), insomnia (5 participants, 33%), and pain in extremity (4 participants, 27%). Beyond the two previously reported serious adverse events (SAEs), one new SAE was reported in the past year that involved a participant with advanced arthritis who was hospitalized for surgery.

Registrational Studies Underway

The global Phase 3 program includes two studies with valoctocogene roxaparvovec, one with the 6e13 vg/kg dose (GENEr8-1) and one with the 4e13 vg/kg dose (GENEr8-2). With the goal of evaluating superiority of valoctocogene roxaparvovec to the current standard of care, prophylactic therapy, the sample size of the GENEr8-1 study is approximately 130 total participants. Enrollment completion in the newly amended GENEr8-1 study is expected in the third quarter of 2019.

GENEr8-2, the ongoing Phase 3 study with the 4e13 vg/kg dose is expected to complete enrollment one to two quarters

after GENEr8-1 in 2020.

BioMarin now has six clinical studies underway in its comprehensive gene therapy program for the treatment of severe hemophilia A. In addition to the two global Phase 3 studies GENEr8-1 and GENEr8-2, 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. Two additional and separate studies, one to study AAV seroprevalence in people with severe hemophilia A and one non-interventional study to determine baseline characteristics in people with hemophilia A, are ongoing around the world. Participants in the Phase 1/2 dose escalation study will continue to be monitored as part of the global program underway.

Valoctocogene roxaparvovec investigational product from BioMarin's commercial scale manufacturing facility is being used in all BioMarin interventional studies.

Regulatory Status

The U.S. Food and Drug Administration (FDA) granted valoctocogene roxaparvovec Breakthrough Therapy Designation. The FDA's Breakthrough Therapy Designation program is intended to facilitate and expedite development and review of new drugs to address unmet medical need in the treatment of a serious condition. To qualify for Breakthrough Therapy Designation, preliminary clinical evidence must show that that the drug may demonstrate substantial improvement over existing therapies.

The European Medicines Agency (EMA) has granted access to its Priority Medicines (PRIME) regulatory initiative for valoctocogene roxaparvovec. To be accepted for PRIME, an investigational therapy has to show its potential to benefit patients with unmet medical needs based on early clinical data. PRIME focuses on medicines that may offer a major therapeutic advantage over existing treatments, or benefit patients with no treatment options. These medicines are considered priority medicines within the European Union (EU).

BioMarin's valoctocogene roxaparvovec has also 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.

Gene Therapy Manufacturing

BioMarin has constructed one of the first gene therapy manufacturing facilities of its kind in the world, which is located in Novato, California. Good Manufacturing Practices (GMP) production of valoctocogene roxaparvovec has commenced, and this manufacturing facility will support pivotal clinical development activities and anticipated commercial demand, if valoctocogene roxaparvovec is approved. This facility is capable of supporting approximately 4,000 doses per year, and the production process was developed in accordance with International Conference on Harmonisation guidance for Pharmaceuticals for Human Use facilitating worldwide registration with health authorities. In 2018, the International Society for Pharmaceutical Engineering (ISPE) selected the Company's gene therapy manufacturing facility as the Facility of the Year Category Winner for Project Execution.

About Hemophilia A

People living with hemophilia A lack enough FVIII protein to help their blood clot and are at risk for painful, potentially life-threatening bleeds from even modest injuries. Additionally, people with severe hemophilia A often experience painful, spontaneous bleeds into their muscles or joints. The standard of care for the 43 percent of individuals with hemophilia A who are severely affected is a prophylactic regimen of Factor VIII infusions administered intravenously two to three times per week. Despite these regimens, many people continue to experience 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 (FVIII) 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 is born with 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. (BioMarin), including without limitation, statements about the development of BioMarin's valoctocogene roxaparvovec program generally; the Phase 1/2 study with valoctocogene roxaparvovec; the impact of valoctocogene roxaparvovec gene therapy for treating people with severe hemophilia A; and the projected durability of valoctocogene roxaparvovec to maintain Factor VIII levels at hemostatic levels. 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; additional data from the continuation of this Phase 1/2 trial, any potential adverse events observed in the continuing monitoring of the participants in the clinical trials; the content and timing of decisions by the U.S. Food and Drug Administration, the European Commission and other regulatory authorities; the content and timing of decisions by local and central ethics committees regarding the clinical trials; errors and deficiencies in our durability modeling; 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, 2019, 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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