BioMarin's Investigational Gene Therapy for Hemophilia A at 6e13 vg/kg Dose Maintains Average Factor VIII Levels within Normal Range for over One Year

SAN RAFAEL, Calif., July 11, 2017 /PRNewswire/ --

- BioMarin Provides BMN 270 Data at International Society on Thrombosis and Haemostasis (ISTH) 2017 Congress
- Initiation of Phase 3 Registrational Study Planned for Q4 2017 with 6e13 vg/kg Dose
- 97% Reduction in Mean Annualized Bleed Rate (ABR) with 6e13 vg/kg Dose Compared to Prophylaxis
- 94% Reduction in Mean Annual Factor VIII Infusions with 6e13 vg/kg Dose Compared to Prophylaxis
- Gene Therapy Facility in U.S. Constructed
- Conference Call and Live Webcast Tuesday, July 11th at 2:30pm CEST/8:30am ET

BioMarin Pharmaceutical Inc. (NASDAQ:BMRN) announced today an update to its previously reported interim results of an open-label Phase 1/2 study of BMN 270, an investigational gene therapy treatment for severe hemophilia A. The updated results will be presented by John Pasi, Ph.D. F.R.C.P, at Barts and the London School of Medicine and Dentistry and Haemophilia Clinical Director at Barts Health NHS Trust and primary investigator for the BMN 270 Phase 1/2 clinical trial, during an oral presentation at the International Society on Thrombosis and Haemostasis (ISTH) 2017 Congress being held July 8-13, 2017 in Berlin, Germany. Professor Pasi will present the data in a late breaking abstract on July 11, 2017, which will be the only clinical data in gene therapy for hemophilia A to be presented at the meeting.

In the open-label Phase 1/2 study, a total of 15 patients with severe hemophilia A [1] (defined by the World Federation of Hemophilia (WFH) as having Factor VIII activity levels less than 1%, expressed as a percentage of normal factor activity in blood) received a single dose of BMN 270, seven of whom were treated at a dose of 6e13 vg/kg and an additional six of whom were subsequently treated at a lower dose of 4e13 vg/kg. The other two patients in the study were treated at lower doses as part of dose escalation in the study and did not achieve therapeutic efficacy. According to the WFH rankings of severity of hemophilia A, the normal range of Factor VIII activity levels for people without disease is between 50% and 150%, expressed as a percentage of normal factor activity in blood, and the mild hemophilia A range of Factor VIII activity levels is between 5% and 40%. (See Table 6 for further information on severity levels)

As of the May 31, 2017 data cutoff, all patients at the 6e13 vg/kg dose had reached 52 weeks of post-treatment follow-up. Median and mean Factor VIII levels from week 20 through 52 for the 6e13 vg/kg dose cohort have been consistently within the normal levels post treatment as a percentage calculated based on

the numbers of International Units per deciliter (IU/dL) of plasma. (See Table 1). At one year after dosing, the median and mean Factor VIII levels of the 6e13 vg/kg cohort continue to be above 50%. (See Table 6)

Table 1: Factor VIII Levels (%) of 6e13 vg/kg Dose Patients* by Visit (N=7)

Week**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**
6e13 vg/kg Dose									
N***	7	7	7	6	7	7	7	7	7
Median Factor VIII Level**** (%)	**97**	**101**	**122**	**99**	**99**	**111**	**105**	**105**	**89**
Mean Factor VIII Level**** (%)	**118**	**129**	**123**	**122**	**116**	**124**	**122**	**106**	**104**
Range (low, high)	(12, 254)	(12, 227)	(15, 257)	(26, 316)	(31, 273)	(17, 264)	(20,242)	(23,196)	(20, 218)

**All patients had severe hemophilia A, defined as less than 1% of Factor VIII activity levels, expressed as a percentage of normal factor activity in blood.*

***Weeks were windowed by +/- 2 weeks*

**** For week 32, one patient had no Factor VIII reading*

*****Bolded numbers are in the normal range of Factor VIII as defined by the World Federation of Hemophilia, http://www.wfh.org/en/page.aspx?pid=643 (link current as of June 30, 2017). Factor VIII levels are determined by one-stage assay.*

The median and mean Factor VIII levels from week 8 to 24 for all patients observed at the 4e13 vg/kg dose are in the mild level. Three of these subjects who have been observed for 24 weeks are at the upper end of mild. (See Table 2 for Factor VIII levels and Table 6 for severity levels)

Table 2: Factor VIII Levels (%) of 4e13 vg/kg Dose Patients* by Visit (N=6)

Week**	**4**	**8**	**12**	**16**	**20**	**24**
4e13 vg/kg Dose						
n	6	6	6	3	3	3
Median Factor VIII Level*** (%)	4	**15**	**21**	**35**	**37**	**33**
Mean Factor VIII Level*** (%)	**5**	**13**	**19**	**33**	**38**	**33**
Range (low, high)	(2,10)	(3,21)	(6,32)	(28,38)	(31,45)	(24,41)

**All patients had severe hemophilia A, defined as less than 1% of Factor VIII activity levels, expressed as a percentage of normal factor activity in blood.*

***Weeks were windowed by +/- 2 weeks*

**** Bolded numbers are in the mild range of Factor VIII as defined by the World Federation of Hemophilia, http://www.wfh.org/en/page.aspx?pid=643 (link current as of June 30, 2017). Factor VIII levels are determined by one-stage assay.*

Annualized Bleed Rate (ABR) and Factor VIII Infusions

For the six patients who were on pre-study prophylaxis after receiving a single dose of BMN 270 at 6e13 vg/kg dose and after reaching a Factor VIII level above 5%, the mean ABR was reduced by 97% from 16.3 to 0.5. The median ABR for those same patients was reduced from 16.5 to zero. The mean annualized Factor VIII infusions were reduced by 94% from 136.7 to 8.5. The median annualized Factor VIII infusions were reduced from 138.5 to zero. The 7th patient was receiving Factor VIII on demand treatment before the study and was not included in this summary. (See Table 3)

Table 3: Summary of Mean Annualized Bleeding Rate (ABR) and FVIII Infusions of 6e13 vg/kg Dose Patients Previously on Prophylaxis (N=6)*

	Before BMN 270 Infusion***	**After BMN 270 Infusion********
	Mean (median, SD)	**Mean (median, SD)**
Annualized Bleeding Rate(bleeding episodes per year per subject)**	16.3 (16.5, 15.7)	0.5 (0.0, 1.1)

Annualized FVIII Infusions** **(infusions per year per subject)**	136.7 (138.5, 22.4)	8.5 (0.0, 20.8)

**A 7th patient received Factor VIII on demand and was not included in analysis.*
***Post infusion data were based on data after Factor VIII levels were above 5%*
****Obtained from medical records.*
*****5 of 6 patients had 0 bleeds requiring Factor VIII infusions and 0 Factor VIII infusions after Factor VIII levels were above 5%.*

For the six patients who were on pre-study prophylaxis after receiving a single dose of BMN 270 at 4e13 vg/kg dose and after reaching a Factor VIII level above 5%, the mean ABR was reduced from 12.2 to zero. The median ABR for those same patients was reduced from 8.0 to zero. The mean annualized Factor VIII infusions were reduced from 144.2 to zero. The median annualized Factor VIII infusions were reduced from 155.5 to zero. (See Table 4)

Table 4: Summary of Mean Annualized Bleeding Rate (ABR) and FVIII Infusions of 4e13 vg/kg Dose Patients Previously on Prophylaxis (N=6)

	Before BMN 270 Infusion**	**After BMN 270 Infusion*****
	Mean (median, SD)	**Mean (median, SD)**
Annualized Bleeding Rate* (bleeding episodes per year per subject)	12.2 (8.0, 15.4)	0.0 (0.0, 0.0)
Annualized FVIII Infusions* **(infusions per year per subject)**	144.2 (155.5, 43.3)	0.0 (0.0, 0.0)

** Post infusion data were based on data after Factor VIII levels were above 5%*
***Obtained from medical records.*
****6 patients had 0 bleeds requiring Factor VIII infusions and 0 Factor VIII infusions after Factor VIII levels were above 5%.*

Quality of Life (QoL)

Patients on the 6e13 vg/kg dose demonstrated improvement in Haemo-QoL-A (HRQOL), a validated health related quality of life measurement tool for patients with hemophilia, as early as 16 weeks with maintenance through 52 weeks after receiving a single dose of BMN 270. By week 16, patients achieved a clinically meaningful difference from baseline with a mean score change of 13.4 with a standard deviation (SD) of 11.2. The minimal clinically important difference (MCID) based on prior studies ranges from 5.2 to 7.9. Patients demonstrated sustained clinically meaningful HRQOL score changes through to week 52 with a mean score change from baseline of 9.6 with an SD of 12.7. (See Table 5). The score improvement

achieved an MCID, which was observed across all six domains tested, *i.e.* Consequences of Bleeding, Physical Functioning, Role Functioning, Emotional Impact, Treatment Concern and Worry.

Table 5: Change from Baseline in Total Health-Related Quality of Life (HRQOL) Score of 6e13 vg/kg Dose Cohort

		6E13 vg/kg Dose Cohort (N=7)	
		Total HRQOL Score	**Change from Baseline**
Baseline	Mean (SD)	71.9 (16.6)	(na)
	Median	76.2	(na)
Week 16	Mean (SD)	85.3 (13.0)	13.4 (11.2)
	Median	84.7	6.0
Week 28	Mean (SD)	84.8 (12.5)	12.9 (13.7)
	Median	87.5	8.0
Week 52	Mean (SD)	81.6 (15.1)	9.6 (12.7)
	Median	86.7	7.0

SD = standard deviation; na = not applicable.

"The data continue to build the clinical case for the potentially groundbreaking impact of BMN 270 gene therapy for treating patients with hemophilia A. Patients at the two highest doses have stopped prophylactic treatment and to date, bleeds have effectively been eliminated," said John Pasi, Ph.D. at Barts and the London School of Medicine and Dentistry and Haemophilia Clinical Director at Barts Health NHS Trust and primary investigator for the BMN 270 Phase 1/2 clinical trial. "In addition to the clinical data showing meaningful improvement in bleeds and Factor VIII levels up to 52 weeks, the quality of life data from the patients at the highest dose demonstrate that the potential clinical benefit could also represent a tangible improvement in a patient's quality of life."

"With this important clinical data, we are moving into a Phase 3 registrational study for BMN 270 gene therapy at the 6e13 vg/kg dose. BMN 270 has demonstrated an unprecedented result in potentially shifting severe hemophilia A patients to the normal range of Factor VIII expression, which is consistent with someone who has no disease," said Hank Fuchs, M.D., President, Worldwide Research and Development at BioMarin. "We are striving to make a big difference for patients with severe hemophilia A by developing a treatment that not only has the potential to eliminate bleeds, but also has the potential to eliminate the requirement for recombinant Factor VIII infusions for hemophilia A patients related to trauma, surgery and day-to-day activities."

Safety

Overall, BMN 270 was well tolerated by patients across all doses. No patients developed inhibitors to Factor VIII and no patients withdrew from the study. The most common adverse events (AEs) across all dose cohorts were alanine aminotransferase (ALT) elevations (10 patients, 67%), arthralgia (7 patients, 47%) and back pain, fatigue, headache (5 patients each, 33%). Two patients reported Serious Adverse Events (SAEs) during the study. One patient was hospitalized for observation after developing Grade 2 pyrexia with myalgia and headache within 24 hours of receiving BMN 270 (4e13 vg/kg dose). The event resolved within 48 hours following treatment with paracetamol, an over-the-counter treatment for pain and fever. The event was assessed as related to BMN 270. The other SAE was assessed as not related to BMN 270, and was attributed to a planned knee surgery to treat hemophilic arthropathy, and Grade 1 in severity. It resolved without any further complications.

AEs of ALT elevation were reported in 10 of the 15 patients. All events of ALT increases were non-serious and as of the data cutoff, seven of the 10 patients had durations of ALT greater than 1.5 times the Upper Limit of Normal (ULN) range from 0.4 to 7 weeks and Grade 1 in severity. All of the seven patients at the 6e13 vg/kg dose remain off of corticosteroids with no lasting significant impact on Factor VIII expression and normal ALT levels. Three of the six patients at the 4e13 vg/kg dose received corticosteroids for ALT increases, one has successfully tapered off corticosteroids and two are tapering off of corticosteroids.

Phase 3 Study and Regulatory Status

BioMarin plans to initiate a Phase 3 registrational study in Q4 2017 for BMN 270. Final determination of the design of the study in severe hemophilia A patients is underway; the study will likely include fewer than 100 patients and collect data for not longer than a year after a single dose of BMN 270 with subsequent long-term follow-up.

The company is moving the 6e13 vg/kg dose forward based on the possibility to get most patients safely into the normal Factor VIII range, which could provide them the opportunity to engage in normal daily activities without concern for spontaneous bleeds or the need for additional Factor VIII due to trauma (including sports and minor injuries) or invasive procedures. However, to evaluate a dose that may have a different drug profile, we will consider doing an additional 4e13 vg/kg dose clinical study later. While we may do further study on a lower dose, by going forward with the 6e13 vg/kg dose now, we hope to bring this novel therapy to patients as quickly as possible.

The European Medicines Agency (EMA) has granted access to its Priority Medicines (PRIME) regulatory initiative for BMN 270. 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).

Gene Therapy Manufacturing

In addition, BioMarin has designed and constructed its first gene therapy manufacturing facility located in Novato, California. Good Manufacturing Practices (GMP) production of BMN 270 is anticipated to commence imminently to support ongoing clinical development activities and if approved, commercial demand.

"BioMarin has built a manufacturing facility that can produce BMN 270 at the scale and quantity to support clinical development and projected commercial demand, if approved," said Robert Baffi, Ph.D., Executive Vice President Technical Operations. "We drew upon our expertise in manufacturing complex biologics to efficiently build one of the largest gene therapy manufacturing facilities in the world, which will allow us to control scheduling, quality and costs to facilitate rapid product development."

Conference Call and Live Webcast to be held Tuesday, July 11th at 2:30pm CEST/8:30am ET

Interested parties may access a live webcast of the conference call via the investor section of the BioMarin website, www.biomarin.com. The Late Breaker slide presentation will be available to download in advance of the call. A replay of the call will be archived on the site for one week following the call.

U.S. / Canada Dial-in Number: (866) 502-9859
International Dial-in Number: (574) 990-1362
Conference ID: 41581309

Replay Dial-in Number: (855) 859-2056
Replay International Dial-in Number: (404) 537-3406
Conference ID: 41581309

Phase 1/2 Study Design

The current Phase 1/2 study is evaluating the safety and efficacy of BMN 270 gene therapy in up to 15 patients with severe hemophilia A defined as less than or equal to 1% of Factor VIII activity levels, expressed as a percentage of normal factor activity in blood. The primary endpoints are to assess the safety of a single intravenous administration of a recombinant AAV vector coding for human-coagulation Factor VIII and to determine the change from baseline of Factor VIII expression level at 16 weeks after infusion. The kinetics, duration and magnitude of AAV-mediated Factor VIII activity in individuals with hemophilia A will be determined and correlated to an appropriate BMN 270 dose.

This is a dose escalation study with the goal of observing an increase in Factor VIII levels. Secondary endpoints include assessing the impact of BMN 270 on the frequency of Factor VIII replacement therapy, the number of bleeding episodes requiring treatment, and any potential immune responses. Patients will be monitored for safety and durability of effect for five years. The study has completed enrollment.

About Hemophilia A

Hemophilia A, also called Factor VIII (FVIII) deficiency or classic hemophilia, is a 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.[2] As an X-linked disorder, hemophilia A mostly affects males, occurring in approximately 1 in 5,000 male births.[3] People living with the disease are not able to form blood clots efficiently and are at risk for excessive bleeding from modest injuries, potentially endangering their life. People with severe hemophilia often bleed spontaneously into their muscles or joints. The standard of care for the 43% of hemophilia A patients who are severely affected, is a prophylactic regimen of Factor VIII infusions three times per week.[4] Even with prophylactic regimens, many patients still experience microbleeds and spontaneous bleeding events that result in progressive joint damage

Table 6: Severity of Hemophilia*

Level	**Factor VIII Level (Percentage of normal factor activity in blood)****	**Description of Severity*****
Normal range	50-150%	
Mild hemophilia	5-40%	People with mild hemophilia usually bleed only as a result of surgery or major injury. They do not bleed often and, in fact, may never have a bleeding problem.
Moderate hemophilia	1-5%	People with moderate hemophilia bleed less frequently, about once a month. They may bleed for a long time after surgery, a bad injury, or dental work. A person with moderate hemophilia will rarely experience spontaneous bleeding.
Severe hemophilia	Less than 1%	People with severe hemophilia usually bleed frequently into their muscles or joints. They may bleed one to two times per week. Bleeding is often spontaneous, which means it happens for no obvious reason.

**Information sourced from World Federation of Hemophilia, http://www.wfh.org/en/page.aspx?pid=643 (link current as of June 31, 2017)*

***Percentage calculated based on the number of international units (IU) per milliliter (ml) of whole blood.*

****Severity describes how serious a problem is. The level of severity depends on the amount of clotting factor that is missing from a person's blood.*

About Gene Therapy at BioMarin

Gene therapy is a treatment designed to alter a genetic problem by adding a corrected copy of the defective gene. The functional gene is inserted into a vector – containing a DNA sequence coding for a specific protein – that acts as a delivery mechanism, providing the ability to deliver the functional gene to cells. The cells can then use the information to build the functional protein that the body needs, potentially reducing or eliminating the cause of the disease. Currently, gene therapy for the treatment of hemophilia A is available only as part of a clinical trial. The AAV approach to gene therapy has been advanced at the University College London (UCL) in the treatment of Hemophilia B. At UCL, the data regarding this technology has demonstrated the ability to correct bleeding and to be generally well tolerated for greater than four years in a continuing clinical trial.

About BioMarin

BioMarin is a global biotechnology company that develops and commercializes innovative therapies for people with serious and life-threatening rare disorders. 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 Statement

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 BMN 270 program generally, the impact of BMRN 270 gene therapy for treating patients with hemophilia A, the potential for BMN 270 to bring Factor VIII levels to normal and to reduce or eliminate bleeds, the planned Phase 3, or other possible future clinical studies of BMN 270. 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 BMN 270, 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 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; our ability to successfully manufacture the product candidate for the preclinical and clinical trials; 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, 2017, 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.

BioMarin® is a registered trademark of BioMarin Pharmaceutical Inc.

[1] Source: World Federation of Hemophilia
http://www.wfh.org/en/resources/annual-global-survey
http://www.wfh.org/en/abd/prophylaxis/prophylaxis-administration-and-dosing-schedules

[2] Source: National Hemophilia Foundation
http://www.hemophilia.org/Bleeding-Disorders/Types-of-Bleeding-Disorders/Hemophilia-A

[3] Source: CDC
http://www.cdc.gov/ncbddd/hemophilia/data.html

[4] Source: World Federation of Hemophilia
http://www.wfh.org/en/resources/annual-global-survey
http://www.wfh.org/en/abd/prophylaxis/prophylaxis-administration-and-dosing-schedules

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