BioMarin Announces Plans to Progress Both the 6e13vg/kg and 4e13 vg/kg Doses of BMN 270, its Investigational Gene Therapy for Hemophilia A, into Phase 3 Studies

- Recent 4e13 vg/kg Data Indicates Majority of Patients in Open-Label Phase 1/2 Study Expected to Achieve Factor VIII Activity Levels in the Normal Range
- Update to be discussed on Second Quarter Financial Results Conference Call Today at 4:30pm ET/1:30pm PT

SAN RAFAEL, Calif., Aug. 2, 2017 /PRNewswire/ -- BioMarin Pharmaceutical Inc. (NASDAQ: BMRN) announced today that it will expand its development plan for BMN 270, its investigational gene therapy for hemophilia A, to include an additional Phase 3 study of the 4e13 vg/kg dose based on updated data as of July 28, 2017 from its ongoing open-label Phase 1/2 study of BMN 270. Since the last data update presented at the International Society on Thrombosis and Haemostasis (ISTH) 2017 Congress, the Factor VIII activity levels in the 4e13 vg/kg cohort have continued to trend upwards and now support an additional Phase 3 study to the development program.

Based on these updated results, BioMarin plans to initiate two separate Phase 3 studies as soon as possible, one with the 4e13 vg/kg dose and one with the 6e13 vg/kg dose. In addition, the Company has commissioned its commercial gene therapy manufacturing facility and expects to start the Phase 3 program in the fourth quarter of 2017.

A total of six patients received a single dose of BMN 270 at the 4e13 vg/kg dose. Based on the most recent data, for the three patients who were given the 4e13 vg/kg dose in November/December 2016, at week 32, all are in or near to the normal range of Factor VIII activity levels, with both median and mean Factor VIII levels of 51%. For the cohort of three patients who were given the 4e13 vg/kg dose in February/March 2017, at week 20, their Factor VIII activity levels have all moved into the mild range and two of the three are continuing to trend upward. For all six patients who received a dose of 4e13 vg/kg, at week 20, the median Factor VIII level was 34% and the mean was 31%. (See Table 1) According to the World Federation of Hemophilia rankings of severity of hemophilia A, the mild hemophilia A range of Factor VIII activity levels is between 5% and 40%, and the normal range of Factor VIII activity levels for people without disease is between 50% and 150%, in each case expressed as a percentage of normal factor activity in blood. (See Table 3 for further information on severity levels)

All six patients who received a single dose of BMN 270 at 4e13 vg/kg dose had severe hemophilia A and had been treated with prophylactic Factor VIII pre-study. After receiving BMN 270 and then reaching a Factor VIII activity level above 5%, through the July 28th data cut, the mean Annualized Bleed Rate (ABR) was reduced by 92% from 12.2 to 1.0. The median ABR for those same patients was reduced from 8.0 to zero. The mean annualized Factor VIII infusions were reduced by 97% from 144.2 to 4.8. The median annualized Factor VIII infusions were reduced from 155.5 to zero. (See Table 2)

"With the additional eight weeks of data for BMN 270 at the 4e13 vg/kg dose, we now plan to move forward as rapidly as possible with two separate Phase 3 studies with the 4e13 vg/kg and the 6e13 vg/kg doses. By concurrently moving both of these doses into Phase 3 development, we have the opportunity to determine if patients may be better served by having one or both of these doses commercially available. BioMarin is well positioned with the resources and manufacturing capacity to undertake the studies necessary to explore both doses to determine the better potential therapeutic option," said Hank Fuchs, M.D., President, Worldwide Research and Development at BioMarin. "Given the low level of pre-existing immunity to AAV5, we expect that approximately 90 percent of patients would be treatment candidates for BMN 270 based on this criteria."

Table 1: Factor VIII Levels (%) of 4e13 vg/kg Dose Patients* by Visit (N=6)

Week**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**
4e13 vg/kg Dose								
n	6	6	6	6	6	3	3	3
Median Factor VIII Level*** (%)	4	**15**	**21**	**29**	**34**	**29**	**41**	**51**
Mean	**5**	**13**	**19**	**26**	**31**	**32**	**39**	**51**

Factor VIII Level*** (%)								
Range (low, high)	(2,10)	(3,21)	(6,32)	(5,38)	(7,45)	(24,42)	(32,44)	(48,54)

**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 to normal range of Factor VIII activity as defined by the World Federation of Hemophilia, http://www.wfh.org/en/page.aspx?pid=643 (link current as of July 31, 2017). Factor VIII levels are determined by one-stage assay.*

Table 2: Summary of Mean Annualized Bleeding Rate (ABR) and FVIII Infusions of 4e13 vg/kg Dose Patients Previously on Prophylaxis (N=6) up to 32 Weeks

	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)	1.0 (0.0, 2.3)
Annualized FVIII Infusions* **(infusions per year per subject)**	144.2 (155.5, 43.3)	4.8 (0.0, 11.6)

** 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 after Factor VIII levels were above 5%.*

Efficacy Data on 6e13 vg/kg Dose as Announced at ISTH July 11, 2017

As of the May 31, 2017 data cutoff, all seven 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, expressed as a percentage of normal factor activity in blood. (See Press Release). At one year after dosing, the median and mean Factor VIII levels of the 6e13 vg/kg cohort continue to be above 50%. After 52 weeks of follow-up, the phase 1/2 study protocol specifies that planned patient visits are reduced in frequency from once a week to once every twelve weeks. Consequently, as of May 31, 2017 when all patients in the 6e13 vg/kg dose had reached 52 weeks of follow up, all patients in the 6e13 vg/kg dose converted to a quarterly follow-up visit schedule.

Safety

Overall, BMN 270 has been well-tolerated by patients across all doses, including the two patients that received the lowest doses of 6e12 and 2e13 vg/kg, respectively. 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) elevation (11 patients, 73%); arthralgia, aspartate aminotransferase elevation, and headache (7 patients each, 47%); back pain and fatigue (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. 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, attributed to a planned knee surgery to treat hemophilic arthropathy, and Grade 1 in severity. No complications were reported.

AEs of ALT elevation were reported in 11 of the 15 patients. All events of ALT elevation were mild (Grade 1) and non-serious. All seven patients at the 6e13 vg/kg dose remain off of corticosteroids with no lasting significant impact on Factor VIII expression and have normal ALT levels. Four of the six patients at the 4e13 vg/kg dose received corticosteroids for ALT elevation, three have successfully tapered off corticosteroids and one is tapering off of corticosteroids.

Phase 3 Study and Regulatory Status

BioMarin plans to initiate two Phase 3 studies with BMN 270, one with a dose of 4e13 vg/kg and the other with 6e13 vg/kg dose. Final determination of the design of the studies in severe hemophilia A patients is underway; the studies will each likely include fewer than 100 patients.

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

BioMarin has designed and constructed one of the largest gene therapy manufacturing facilities in the world, which is located in Novato, California. Good Manufacturing Practices (GMP) production of BMN 270 is anticipated to commence imminently to support ongoing clinical development activities and for anticipated commercial demand.

Conference Call and Live Webcast to be held Wednesday, August 2 at 4:30pm ET/1:30pm PT

Interested parties may access a live webcast of the conference call via the investor section of the BioMarin website, www.biomarin.com. 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: 41574149

Replay Dial-in Number: (855) 859-2056
Replay International Dial-in Number: (404) 537-3406
Conference ID: 41574149

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.

Along with assessing safety, this dose escalation study is designed to observe 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.[1] As an X-linked disorder, hemophilia A mostly affects males, occurring in approximately 1 in 5,000 male births.[2] 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.[3] Even with prophylactic regimens, many patients still experience microbleeds and spontaneous bleeding events that result in progressive joint damage

Table 3: 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	Less than 1%	People with severe hemophilia usually bleed frequently into their muscles or

hemophilia		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 July 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 supports 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.BMRN.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 long term effect of treatment with BMN 270, expected design of future clinical trials, and the expected regulatory actions related to 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; the continued clinical experiences of the patients in the current studies; 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.

[1] Source: National Hemophilia Foundation
http://www.hemophilia.org/Bleeding-Disorders/Types-of-Bleeding-Disorders/Hemophilia-A
[2] Source: CDC
http://www.cdc.gov/ncbddd/hemophilia/data.html
[3] 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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