BioMarin to Provide Update to Proof-of-Concept Data for BMN 270 Gene Therapy in Hemophilia A at 35th Annual J.P. Morgan Healthcare Conference

Factor VIII Levels Maintained for All High Dose Patients at 34-50 Weeks
Median Factor VIII Levels of High Dose Cohort within Normal Range
Mean Annualized Bleed Rate Declined 91% for Patients Previously on Prophylactic Factor VIII
All Patients Off Steroids

SAN RAFAEL, Calif., Jan. 8, 2017 /PRNewswire/ -- BioMarin Pharmaceutical Inc. (NASDAQ:BMRN) announced today an update to its positive interim results of an open-label Phase 1/2 study of BMN 270, an investigational gene therapy treatment for severe hemophilia A, which will be presented as part of a company overview at the 35th Annual J.P. Morgan Healthcare Conference in San Francisco, Calif. These data are an update from previously reported results presented in July 2016.

A total of nine patients with severe hemophilia A received a single dose of BMN 270, seven of whom have been treated at the highest dose of 6×10^{13} vg/kg. As of the Dec. 9, 2016 data cutoff, post-treatment follow-up ranges from 34 to 50 weeks. Median Factor VIII levels for the high dose cohort have been consistently within the normal range from 20 weeks through 44 weeks of treatment. (See Table 1) For those seven patients, as of each patient's most recent reading, six of seven patients continue to have Factor VIII levels above 50%, as a percentage calculated based on the numbers of International Units per deciliter (IU/dL) of plasma, and the seventh continues to be above 15%. (See Table 2)

For the six patients at the high dose and previously on a Factor VIII prophylactic regimen, the mean annualized bleeding rate dropped 91% from 16.3 before the BMN 270 infusion to 1.5 two weeks after being dosed (median annualized bleeding rate dropped from 16.5 to 0). For those same six patients, the mean annualized Factor VIII infusions fell 98% from 136.7 to 2.9 (median annualized Factor VIII infusions fell from 138.5 to 0). (See Table 3)

Since the last update, six of the seven patients at the high dose as of the most recent reading are within the normal alanine aminotransferase (ALT) range, and one patient is less than 5% above the upper limit of normal, which is 43 U/L for the central laboratory in this study. (See Table 4) Patients successfully tapered off of steroids with no lasting significant impact on Factor VIII expression or ALT levels. The requirement for prophylactic corticosteroids has been removed for all newly enrolled patients in this study.

Study medication was generally well tolerated. No serious adverse events were observed, and most common adverse events were mild in severity.

The next steps for the program are to begin a potentially registration enabling Phase 2b study in 3Q 2017. In addition, the company is expected to commission its commercial gene therapy manufacturing facility by mid-2017.

"These data continue to show promising evidence that restoration of clotting function can be achieved by gene therapy," said John Pasi, Ph.D. F.R.C.P, Professor of Haemostasis and Thrombosis at Barts and the London School of Medicine and Dentistry and primary investigator for the BMN 270 Phase 1/2 clinical trial. "The increase in Factor VIII levels we have seen has the potential to stop patients bleeding and has changed how we think about treating hemophilia. For the first time we can truly start considering the opportunity for our patients to live a more normal life."

"We are proud that we have been successful in establishing a leadership position in gene therapy for the most common form of hemophilia, and we are intent on initiating potentially registration enabling trials to provide patients with a new treatment option," said Hank Fuchs, M.D., President, Worldwide Research & Development at BioMarin. "To see data that shows a 91 percent drop in the mean annualized bleeding rate and a 98 percent drop in prophylactic infusions coupled with mean and median Factor VIII expression levels in the normal range opens up an exciting treatment possibility for hemophilia A patients."

Table 1: Factor VIII Levels (%) of High Dose Patients* by Visit (N=7)

Week**	**20**	**24**	**28**	**32**	**36**	**40**	**44**
n***	7	7	7	6	7	6	2
Median Factor VIII Level**** (%)	**97**	**101**	**122**	**99**	**99**	**115**	**119**
Mean Factor VIII Level**** (%)	**118**	**130**	**124**	**122**	**115**	**127**	**119**
Range (high, low)	(12, 254)	(16, 227)	(15, 257)	(26, 316)	(31, 273)	(17, 264)	(105, 133)

**All patients had severe hemophilia A defined as equal to or less than 1% of blood clotting factor.*

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

****For week 32, one patient had no Factor VIII reading, for week 40, one patient had not reached week 40 and for week 44, only 2 patients reached a week 44 reading*

*****Bolded numbers are in 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 Jan. 8, 2017). Factor VIII levels are determined by one-stage assay.*

Table 2: Summary of Factor VIII Level (%) of High Dose Patients at Most Recent Evaluation (N=7)

High-dose Subject #	**FVIII level (%) at last update in July 2016**	**Most recent week of observation**	**FVIII level (%) at most recent observation**
1	89	50	121
2	219	42	133
3	271	40	222
4	12	41	16

5	133	40	175
6	69	38	77
7	79	34	62

Table 3: Summary of Annualized Bleeding Rate (ABR) and FVIII Infusions of High 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 subject per year)	16.3 (16.5, 15.7)	1.5 (0, 3.8)
Annualized FVIII Infusions* (infusions per subject per year)	136.7 (138.5, 22.4)	2.9 (0, 7.0)

** Rates were based on data from week 3 after BMN270 infusion through last follow-up visit*

***Obtained from medical records.*

****5 of 6 patients had 0 bleeds requiring Factor VIII infusions and 0 Factor VIII infusions from Week 3 after BMN 270 infusion.*

Table 4: Summary of ALT Levels in High Dose Patients at Most Recent Evaluation (N=7)

	ALT (U/L); (ULN = 43 (U/L))		
High-dose Subject#	**Peak ALT level**	**ALT Level at Most Recent Observations**	**ALT Level Status**
1	60	15	Normal
2	95	16	Normal
3	82	42	Normal
4	87	33	Normal
5	43	38	Normal
6	81	45	<1.1 ULN
7	66	27	Normal

All patients currently off steroids.

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 blood clotting factor. 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.

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 5: 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 Jan. 8, 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

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, this technology has shown evidence to be both safe and effective, correcting bleeding for greater than four years in a continuing clinical trial.

Live Webcast on Monday, Jan. 9 at 8:30 am PT, or 11:30 am ET

On Monday, January 9, 2017 at 8:30 am PT, or 11:30 am ET, in San Francisco, California, Jean-Jacques Bienaimé, Chairman and Chief Executive Officer, will present the updated data from an ongoing Phase 1/2 study of BMN 270 gene therapy in hemophilia A along with other company updates. To access the live webcast, please visit the investor section of the BioMarin website. A replay will also be archived on the site for at least one week following the event.

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 five 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 and the timing and results of the clinical trial 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 factors detailed in BioMarin's filings with the Securities and Exchange Commission, including, without limitation, the factors contained under the caption "Risk Factors" in BioMarin's 2015 Annual Report on Form 10-K, and the factors contained in BioMarin's reports on Form 10-Q. 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.

[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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