BioMarin Provides Encouraging Preliminary Data on First 8 Patients in Hemophilia A Gene Therapy Program

Two High Dose Patients Show Increasing Levels of Factor VIII Above 50%
Five of Six High Dose Patients Show Factor VIII Levels Above 5%

SAN RAFAEL, Calif., April 20, 2016 (GLOBE NEWSWIRE) -- BioMarin Pharmaceutical Inc. (NASDAQ:BMRN) announced today preliminary data from an ongoing Phase 1/2 clinical trial with BMN 270, an investigational gene therapy treatment for hemophilia A. A total of eight patients with severe hemophilia A received a single dose of BMN 270, six of whom have been treated at the highest dose of 6×10^{13} vg/kg, and to date, post-treatment follow-up ranges from five to 16 weeks. At last observation, patients at the highest dose experienced increasing Factor VIII activity levels ranging between 4% and 60% (as a percentage calculated based on the numbers of International Units (IU) per milliliter of whole blood), with five of six patients treated at the high dose now over 5% and two of six at over 50%. (See Table 1) All high dose patients improved from severe to either moderate, mild or normal range in terms of factor levels based on World Federation of Hemophilia criteria. (See Table 2)

Liver function tests have been monitored closely during the course of the trial. The first three patients were not administered prophylactic corticosteroids. Two of these patients experienced elevated alanine aminotransferase (ALT) levels. Patient 3, the first patient treated at the highest dose level, experienced a mild ALT elevation at week 4, which prompted administration of a course of corticosteroids. ALT levels in this patient continued to rise modestly during the corticosteroid therapy, which was completed at week 14. Two weeks later a new corticosteroid regimen was initiated when ALT levels became minimally abnormal for the first time. The expression of Factor VIII continued to increase during this elevation of ALT and is currently at 57%. In addition, 28 weeks after dosing, Patient 1 treated at the lowest dose experienced a rise in ALT level to 128 IU/L, although this patient had never documented Factor VIII expression above 1%. After the third patient, all patients were to be started on prophylactic corticosteroid therapy and to date no further patients have experienced abnormal ALT levels. BioMarin plans to discuss these findings with UK regulatory authorities prior to dosing the remaining patients.

"We are encouraged by this early data on BMN 270 and the trend we are seeing in increasing Factor VIII levels over time. BMN 270 could have the potential to reduce and possibly eliminate the need for infusions of Factor VIII," said Hank Fuchs, M.D., Chief Medical Officer at BioMarin.

"If BMN 270 allows hemophilia A patients to maintain around 5% of normal levels of Factor VIII, it could have a real and meaningful clinical benefit by reducing the need for Factor VIII infusions and spontaneous bleeds," 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. "I am looking forward to further assessing the data over the 16 weeks and beyond in this ongoing study."

Patients with hemophilia A are not able to produce enough functional Factor VIII to prevent bleeding and are currently treated with prophylactic or on-demand infusions of plasma-derived or recombinant Factor VIII. BMN 270 is designed to address the underlying genetic defect that prevents the expression of functional Factor VIII by using an adeno-associated virus (AAV) vector to deliver a functional copy of the factor VIII gene to a patients' own cells with the aim of a single infusion of BMN 270 providing a long-lasting increase in Factor VIII levels.

BMN 270 has received orphan drug designation from the European Commission and U.S. Food and Drug Administration. Phase 3 design preparation and high volume manufacturing plans are underway.

Table 1: Summary of 8 Patients Factor VIII Levels at Most Recent Evaluations

Patient #	Dose*	Most Recent Week of Observation	Percentage Factor VIII activity	Severity of Hemophilia at Latest Measurement**
1	Low	20	< 1	Severe
2	Medium	16	2	Moderate
3	High	16	57	Normal
4	High	8	60	Normal
5	High	7	8	Mild
6	High	7	4	Moderate
7	High	6	21	Mild
8	High	5	10	Mild

* Low = (6 x 10^{12} vg/kg), Medium = (2 x 10^{13} vg/kg), High = (6 x 10^{13} vg/kg)
** Information sourced from World Federation of Hemophilia, http://www.wfh.org/en/page.aspx?pid=643 (link current as of April 20, 2016)

Table 2: Severity of Hemophilia*

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 April 20, 2016)
**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.

Study Design

The current Phase 1/2 study is evaluating the safety and efficacy of BMN 270 gene therapy in up to 12 patients with severe hemophilia A. 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, hemophila 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 percent 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.

About Gene Therapy

Gene therapy is a treatment designed to fix a genetic problem by adding a corrected copy of the defective gene. The functional gene is inserted into a vector - containing a small DNA sequence - 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 proteins 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.

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; outcome of the safety analysis following Patient 1's elevated ALT levels; the content and timing of decisions by the U.S. Food and Drug Administration, the European Commission and other regulatory authorities; 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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