BioMarin InvestorRoom

BioMarin Announces Positive Results From Phase 2A Clinical Study of 6R-BH4 in Sickle Cell Disease

Subjects Show Improvement in Endothelial Dysfunction
Conference Call and Webcast to Be Held Today at 5:00 p.m. ET (22:00 CET)

PRNewswire-FirstCall
NOVATO, Calif.

BioMarin Pharmaceutical Inc. today announced results from its Phase 2a multi-center, open-label, dose-escalation clinical study of 6R-BH4 in patients with sickle cell disease (SCD) designed to evaluate whether 6R-BH4 can improve the endothelial dysfunction observed in SCD patients. Oral administration of 6R-BH4 was associated with an improvement in endothelial dysfunction in sickle cell disease patients.

Key findings from the study:

-- Endothelial dysfunction, measured using the EndoPAT device to assess peripheral arterial tonometry (PAT), was common in the sickle cell disease patient population. At baseline, 56% of the patients in the trial had endothelial dysfunction (PAT score less than or equal to 1.67), consistent with prior studies using other methods for measuring endothelial function.
-- Endothelial dysfunction in SCD patients treated with escalating doses of 6R-BH4 showed improvement at week 8 (5 mg/kg; p=0.042), week 12 (10mg/kg; p=0.003) and week 16 (20 mg/kg; p=0.075).
-- SCD patients with an abnormal PAT scores of less than or equal to 1.67 at baseline demonstrated greater improvement at all dose levels (2.5, 5, 10 and 20 mg/kg).
-- The mean endothelial function PAT score improved from the abnormal to the normal range (>1.67) in SCD patients with an abnormal PAT score at baseline.
-- Improvement in endothelial dysfunction appeared to be dose-dependent.
-- 6R-BH4 was well-tolerated in sickle cell disease patients.

Pending feedback from the FDA at a pre-IND meeting in November, future development plans could include a cross-sectional study in sickle cell disease patients to assess the relationship between endothelial dysfunction and the frequency and severity of sickle cell crises, and a three month double-blind, placebo-controlled dose finding study with a primary endpoint of improvement in endothelial function.

Emil Kakkis, M.D., Ph.D., Chief Medical Officer of BioMarin stated, "We are very encouraged by the study results as it suggests that the known severe endothelial dysfunction present in sickle cell disease patients is due to an acquired BH4 deficiency and is responsive to 6R-BH4 replacement therapy. Endothelial dysfunction in SCD is now believed to play a greater role in the pathophysiology of sickle cell vasoocclusive crises than had previously been realized. The ability to reverse this dysfunction with oral 6R-BH4 therapy represents a new opportunity to treat SCD."

Dr. Kakkis continued, "The EndoPAT device is a new reproducible method to measure the effect of endothelial dysfunction on small vessel function and has been adopted by the ongoing Framingham study of cardiovascular risks and outcomes as recently published. The PAT score has been shown to correlate with other cardiovascular risk factors and endothelial dysfunction in general has been shown to predict adverse cardiovascular events in at least 10 prospective studies. With this current SCD study, we have an indication that 6R-BH4 is active in improving endothelial function, and we hope to establish a clear relationship between the degree of endothelial dysfunction and the frequency and severity of sickle cell crises using a survey of SCD patients with the EndoPAT test."

"Sickle cell disease is a chronic, lifelong disease that affects a significantly large population of approximately 100,000 people in the U.S. These patients suffer periods of intense pain, poor blood flow, organ damage and other serious medical complications. To date, however, there are very limited treatment options for this debilitating disease and average life expectancy is only in the forties," said Lewis Hsu, M.D., Ph.D., Associate Professor of Pediatric Hematology & Interim Director of Marian Anderson Comprehensive Sickle Cell Center, St. Christopher's Hospital for Children, Drexel University College of Medicine, Philadelphia, PA. "These study findings are significant and support the concept of using BH4 to treat sickle cell disease, a somewhat novel but

plausible approach. Recent reviews of the pathophysiology in sickle cell disease have shifted the focus away from the physical sickling of red blood cells and more toward the deteriorating health of the blood vessels resulting from hemolysis and the release of hemoglobin from red cells."

Study Design

The Phase 2a multi-center, open-label study enrolled 32 subjects and was conducted at 12 U.S. sites. Among other eligibility criteria, to participate in the study, SCD patients were at least 15 years of age and were not receiving hydroxyurea or hypertransfusion therapy. Study patients received 6R-BH4 at 2.5 mg/kg, 5 mg/kg, 10 mg/kg and 20 mg/kg for four weeks each in a 16-week dose-escalation study. A total of 21 patients completed the baseline and final assessments.

The primary objective in the study was to evaluate the safety of oral 6R-BH4 administered in escalating doses in patients with sickle cell disease. The secondary objective was to evaluate changes in physiological and biochemical markers of endothelial function which underlie some key aspects of SCD. PAT scores were measured at the end of each 4 week dose period and compared to the baseline PAT score for statistical purposes.

Abstract at American Society of Hematology Conference

Abstract: Peripheral Arterial Tonometry Assessment of Endothelial Dysfunction in Sickle Cell Patients

First Author: Lewis Hsu, M.D., Ph.D.
Date: December 7, 2008
Poster Presentation Time: 6:00 p.m.-8:00 p.m.

Conference Call Information

BioMarin will hold a conference call today, October 15, 2008, at 5:00 p.m. ET to discuss the results of the Phase 2a study of 6R-BH4 in sickle cell disease. This event can be accessed on the investor section of the BioMarin website at http://www.bmrn.com/.

Date: October 15, 2008
Time: 5:00 p.m. ET
U.S. and Canada Toll-Free Dial in #: 866.356.4123
International Dial in #: 617.597.5393
Participant Code: 75782382
Replay Toll-Free Dial in #: 888.286.8010
Replay International Dial in #: 617.801.6888
Replay Code: 73130467

About 6R-BH4

6R-BH4, commonly known as BH4 or tetrahydrobiopterin, is a naturally occurring enzyme cofactor that is required for numerous biochemical and physiologic processes, including the synthesis of nitric oxide (NO). NO has been shown to play a key protective role throughout the cardiovascular system and produces multiple positive effects, such as relaxing smooth muscle, reducing blood pressure, controlling inflammation and reducing platelet aggregation. Researchers have demonstrated that a deficiency of BH4 can disrupt NO synthesis, resulting in a loss of normal endothelial NO production. This loss of endothelial NO production, commonly referred to as endothelial dysfunction, has been associated with many cardiovascular diseases, including hypertension, diabetic vascular disease, peripheral arterial disease, coronary arterial disease and pulmonary hypertension, and has been shown to be a strong predictor of cardiovascular adverse events in a number of clinical studies.

About BioMarin

BioMarin develops and commercializes innovative biopharmaceuticals for serious diseases and medical conditions. The company's product portfolio comprises three approved products and multiple clinical and pre-clinical product candidates. Approved products include Naglazyme(R) (galsulfase) for mucopolysaccharidosis VI (MPS VI), a product wholly developed and commercialized by BioMarin; Aldurazyme(R) (laronidase) for mucopolysaccharidosis I (MPS I), a product which BioMarin developed through a 50/50 joint venture with Genzyme Corporation; and Kuvan(R) (sapropterin dihydrochloride) Tablets, a product for the treatment of phenylketonuria (PKU), developed in partnership with Merck Serono, a division of Merck KGaA of Darmstadt, Germany. Other product candidates include 6R-BH4 for cardiovascular indications, which is currently in Phase 2 clinical development for the treatment of peripheral arterial disease and sickle cell disease, and PEG-PAL (PEGylated recombinant phenylalanine ammonia lyase), which is currently in Phase 1 clinical development for

the treatment of PKU. For additional information, please visit http://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: expectations related to BioMarin's clinical trials of 6R-BH4 for sickle cell disease and other indications, actions by regulatory authorities and the general development of BH4 for sickle cell. 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; the ability to enroll patients in future trials in a timely manner; the actual correlation between PAT scores and clinical endpoints; the content and timing of decisions by the U.S. Food and Drug Administration, the European Commission and other regulatory authorities concerning each of the described products and product candidates; the market for each of these products; 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 2007 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.

Contact:
Investors
Eugenia Shen
BioMarin Pharmaceutical Inc.
(415) 506-6570

Media
Susan Berg
BioMarin Pharmaceutical Inc.
(415) 506-6594

First Call Analyst:
FCMN Contact: eshen@bmrn.com

SOURCE: BioMarin Pharmaceutical Inc.

CONTACT: Investors, Eugenia Shen, +1-415-506-6570, or Media, Susan Berg, +1-415-506-6594, both of BioMarin Pharmaceutical Inc.

Web site: http://www.bmrn.com/
