BioMarin Provides Program Update on Vosoritide in Achondroplasia

New Data Shows Durable and Consistent Effects on Mean Annualized Growth Velocity for up to 12 months with Increases of 46%-65% from Baseline
Phase 3 Randomized Controlled Study Planned to Start at End of 2016

SAN RAFAEL, Calif., April 20, 2016 (GLOBE NEWSWIRE) -- BioMarin Pharmaceutical Inc. (NASDAQ:BMRN) today provided an update on its Phase 2 study of vosoritide, an analog of C-type Natriuretic Peptide (CNP), in children with achondroplasia, the most common form of dwarfism. After 12 months of daily dosing at 15 µg/kg/day, the cohort 3 patients (n=10) experienced a 46% or 1.9 cm/year increase in mean annualized growth velocity from baseline (p-value = 0.02). (See Table 2). These findings provide evidence of durability of effect consistent with previously presented 6-month data for these patients, which demonstrated an annualized increase of 50% or 2.0 cm/year in mean annualized growth velocity. In addition, 6-month data for 12 patients who were initiated on a lower dose and switched to 15 µg/kg/day showed an increase of 65% or 2.3 cm/year in mean annualized growth velocity from baseline (p-value = 0.002).

Vosoritide at 15 µg/kg/day was well tolerated and there were no treatment-related serious adverse events or adverse events leading to discontinuation. Consistent with the initial 6-month data, in the newly released data, all adverse events assessed as related to study drug were mild to moderate. Over 12 months of dosing at 15 µg/kg/day, injection site reactions and hypotension (asymptomatic decreases in blood pressure) were the most common drug related adverse events, reported by 90% and 40% of cohort 3 patients, respectively. All injection site reaction events were mild and the majority were resolved in one hour. All adverse events of hypotension were mild, transient and resolved without intervention. Safety data from lower dose cohort subjects who increased their dose to 15 µg/kg/day for at least 6 months was generally comparable to the 12-month safety data; however, two subjects experienced symptomatic events associated with a decrease in blood pressure, only one of which was deemed by the investigator to be related to study drug. Both subjects continued to receive their daily dose of vosoritide without dose modification. The phase 2 study is also evaluating a higher dose of 30 ug/kg/day. Preliminary data after several months of treatment has shown that this dose is similarly well tolerated with no new safety findings.

A consistent effect in increasing urinary cyclic guanosine monophosphate (cGMP), a urinary pharmacodynamic biomarker, provides further evidence of durable pharmacologic activity of the 15 µg/kg/day dose over the 12-month observation period in cohort 3.

"We're encouraged by the consistency of the data from six to 12 months in both safety and efficacy, and plan to initiate a Phase 3 study by the end of the year," said Hank Fuchs, MD, Chief Medical Officer at BioMarin. "By addressing the root cause of achondroplasia with vosoritide treatment and normalizing annualized growth velocity in children with achondroplasia, we ultimately hope to improve the medical complications of disproportionate bone growth."

"Children with achondroplasia are likely to experience a variety of medical complications caused by the condition," said Ravi Savarirayan, M.D., Ph.D. Professor, Department of Paediatrics, University of Melbourne and Lead Investigator for the vosoritide Phase 2 study. "A treatment like vosoritide has the potential to decrease medical complications and to increase function and quality of life."

While the Phase 2 efficacy endpoint centers on mean annualized growth velocity, BioMarin hopes that that longer treatment may lead to improvement in many of the complications that can be associated with achondroplasia, such as disproportionality, though longer time of treatment and/or a controlled study may be required to demonstrate this effect.

By the end of 2016, BioMarin is planning to initiate a single Phase 3 randomized controlled study over 12 months in children with achondroplasia ages 5-14 with a subsequent long-term open-label extension subject to discussions with regulatory authorities. In addition, BioMarin is planning a separate Phase 2 study evaluating the effect of vosoritide in infants and toddlers. Vosoritide has Orphan designation in both the United States and Europe.

Table 1: Subject Disposition and Demographics

Category	**Cohort 3 (n=10)**	**Cohorts 1 and 2 (n=12)***
Subjects Enrolled and Treated at 15 µg/kg/day	10 (100 %)	12 (100%
Subjects Who Completed 6 Months at 15 µg/kg/day	10 (100%)	12 (100%)
Subjects Who Completed 12 Months at 15 µg/kg/day	10 (100%)	N/A
Age (years) at Enrollment		

Mean (SD)	8.0 (1.63)	7.6 (1.88)
Min, Max	6, 11	5, 10
Gender (n, %)		
Male	4 (40%)	6 (50%)
Female	6 (60%)	6 (50%)

*Subjects increased dose to 15 µg/kg/day after at least 6 months at 2.5 and/or 7.5 µg/kg/day; 4 of original 16 subjects in Cohorts 1 and 2 did not initiate dosing at 15 µg/kg/day due to subject decision to withdraw from the study (2), declining extension study (1), and growth plate closure (1)

Table 2: Vosoritide Summary of Efficacy Results from Phase 2 Study in Children with Achondroplasia

Efficacy Analysis: Annualized Growth Velocity			
Time Point	**6 Months**	**12 Months ** **	**6 Months**
Annualized Growth Velocity	**Cohort 3** 15 µg/kg/daily **(n=10)**	**Cohort 3** 15 µg/kg/daily **(n=10)**	**Cohorts 1, 2** 15 µg/kg/daily **(n=12)**
Baseline			
Mean (SD), cm/Year	4.0 (2.3)	4.0 (2.3)	3.6 (0.96)
Median	4.1	4.1	3.5
Post-Treatment			
Mean, (SD), cm/year	6.1 (1.1)	5.9 (0.92)	5.9 (1.6)
Median	5.9	5.6	5.6
Change from Baseline			
Mean (SD), cm/year	**2.0 (2.0)**	**1.9 (2.0)**	**2.3 (1.9)**
Nominal p-value*	**0.01**	**0.02**	**0.002**
Percent increase from Baseline Based on means (%)	**50 %**	**46 %**	**65 %**

* Nominal p-value, not adjusted for multiplicity
** Mean Annualized Growth Velocity change from baseline increases to 2.0 cm/year (50% increase) if one patient who missed majority of doses between 6 and 12 months is excluded

Phase 2 Study Design

Children in this study completed a minimum six month natural history 901 study to determine their respective baseline growth velocity prior to entering the Phase 2 study with vosoritide. The Phase 2 trial was an open-label, sequential cohort dose-escalation study of vosoritide in children with achondroplasia. In this three dose cohort study, patients were treated with either 2.5 µg/kg/daily, 7.5 µg/kg/ daily or 15 µg/kg/ daily, respectively. A total of 26 children with achondroplasia with an average age of 7.8 years were enrolled in the study. Based on the safety profile observed to date across the three dose cohorts, all subjects participating in the Phase 2 study were offered the dose of 15 µg/kg/daily during the 18 month extension study. An additional 9 patients were enrolled into a fourth cohort of 30 µg/kg/daily at the end of last year and initial growth velocity data from this cohort will be reported later this year.

About Achondroplasia

Achondroplasia, the most common form of human dwarfism, is characterized by failure of normal conversion of cartilage into bone, which results in disproportionate short stature. This condition is caused by a mutation in the fibroblast growth factor receptor 3 gene (FGFR3), a negative regulator of bone growth. Beyond disproportionate short stature, people with achondroplasia can experience serious health complications, including foramen magnum compression, sleep apnea, bowed legs, mid-face hypoplasia, permanent sway of the lower back, spinal stenosis and recurrent ear infections. Some of these complications can result in invasive surgeries such as spinal cord decompression and straightening of bowed legs. In addition, studies show increased mortality at every age.[i][ii]

More than 80% of children with achondroplasia have parents of average stature and have the condition as the result of a spontaneous gene mutation. The worldwide incidence rate of achondroplasia is about one in 25,000 live births, per the World FactBook 2014 edition which translates into approximately 96,000 potential patients. Vosoritide is being tested in children whose growth plates are still "open," typically those under 18 years of age. This is approximately 25 percent of people with achondroplasia. In the United States, Europe, Latin American and the Middle East, there is currently no licensed medicines for achondroplasia.

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 Vosoritide; the continued clinical development of vosoritide; the final results of the Phase 2 trial of vosoritide, the final results of the planned Phase 3 and Phase 2 studies and actions by regulatory authorities. 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 vosoritide; our ability to successfully manufacture vosoritide; the content and timing of decisions by the U.S. Food and Drug Administration, the European Commission and other regulatory authorities concerning vosoritide; 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.

[i] Hecht JT, Francomano CA, Horton WA, Annegers JF. *Am J Hum Genet*. 1987; 41: 454-464.

[ii] Wynn J, King TM, Gabello MJ, Waller DK, Hecht JT. *Am J Med Genet A.* 2007; 143A: 2502-2511.

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