# BioMarin Presents Vosoritide Data in Achondroplasia at American Society of Human Genetics (ASHG) 2016 Meeting

**Highest Dose (30 µg/kg/day) Shows Approximately 50% Increase in Mean Annualized Growth Velocity, Comparable with 15 µg/kg/day dose**
**Consistent Safety Profile at High Dose**
**Findings Support 15 µg/kg/day in Phase 3, Randomized Controlled Study to Start by End of 2016**

SAN RAFAEL, Calif., Oct. 19, 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, at the American Society of Human Genetics 2016 Meeting. Results from 8 children in cohort 4, who completed six months of daily dosing at 30 µg/kg/daily experienced a 46% or 2.1 cm/year increase in mean annualized growth velocity from baseline (p-value = 0.03). These data are comparable to those observed at the lower dose of 15 µg/kg/day in cohort 3. Results from 10 children in cohort 3, who completed six months of daily dosing at 15 µg/kg/day experienced a 50% or 2.0 cm/year increase in mean annualized growth velocity from baseline (p-value = 0.01). (See Table 2.)

Vosoritide was generally well tolerated at all doses. The majority of adverse events (AEs) were mild and no serious AEs were reported as study drug-related. Across all doses, injection site reactions and hypotension were the most common drug-related AEs. All injection site reaction events were mild and transient. AEs of hypotension were mild, transient and resolved without medical intervention, and the majority were asymptomatic and reported in context of routine blood pressure measurements. No new safety findings were observed at the 30 µg/kg/day dose.

"Studying the higher dose in Phase 2 informed the design of our Phase 3 study in vosoritide. While vosoritide at the higher dose of 30 µg/kg/day was generally well-tolerated, the data support our use of the lower dose of 15 µg/kg/day in the Phase 3 study," said Hank Fuchs, MD, Chief Medical Officer at BioMarin. "We believe that growth velocity is an important measurement in developing vosoritide, which has the potential to address the complications associated with achondroplasia. We are grateful to the children and their families who are participating in this study."

"Vosoritide represents a potential, first-of-its-kind treatment for this form of dwarfism, and these clinical studies could provide new insights into improved management of this condition," said Julie Hoover-Fong Director, Greenberg Center for Skeletal Dysplasias, Johns Hopkins University and lead author of the poster of the Vosoritide Phase 2 data update at ASHG.

By the end of 2016, BioMarin intends to initiate a one-year, randomized, placebo-controlled Phase 3 study in children with achondroplasia ages 5-14 with a subsequent open-label extension. Children in this study will have completed a minimum six-month natural history study to determine their respective baseline growth velocity prior to entering the Phase 3 study. The company believes based on discussions with global health authorities that change in growth velocity from baseline as an endpoint could lead to registration. The company plans to augment these data with supportive evidence concerning proportionality and functionality. As is often the case, discussion of ancillary evidence, such as final adult height to be collected, is ongoing. 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: Phase 2 Trial Disposition and Demographics**

| **Category** | **Cohorts 1 and 2** Switched to **15** µg/kg/day **(n=12)*** | **Cohort 3** **15** µg/kg/day **(n=10)** | **Cohort 4** 30 µg/kg/day **(n=9)**** |
|---|---|---|---|
| Children Enrolled and Treated at 15 µg/kg/day | 12 (100%) | 10 (100 %) | 9 (100%) |
| Children Who Completed 6 Months at 15 µg/kg/day | 12 (100%) | 10 (100%) | N/A |
| Children Who Completed 12 Months at 15 µg/kg/day | N/A | 10 (100%) | N/A |
| Children Who Completed 6 Months at 30 µg/kg/day | N/A | N/A | 8 (89%) |
| Age (years) at Enrollment | | | |
| Mean (SD) | 7.6 (1.88) | 8.0 (1.63) | 6.9 (1.17) |
| Min, Max | 5, 10 | 6, 11 | 5, 8 |

| Gender (n, %) | | | |
|---|---|---|---|
| Male | 6 (50%) | 4 (40%) | 4 (44%) |
| Female | 6 (50%) | 6 (60%) | 5 (56%) |

*Children 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)
**One child in cohort 4 discontinued from treatment due to finding of a rare congenital abnormality of conduction identified on routine study of ECG monitoring, which was not associated with symptoms, and patient was removed from treatment for precautionary reasons.

**Table 2: Phase 2 Summary of Efficacy Results in Children with Achondroplasia**

**Efficacy Analysis: Annualized Growth Velocity**

| **Time Point** | **6 Months** | **12 Months ** | **6 Months** | **6 Months** |
|---|---|---|---|---|
| **Annualized Growth Velocity** | **Cohorts 1, 2** 15 µg/kg/daily **(n=12)** | **Cohort 3** 15 g/kg/daily **(n=10)** | **Cohort 3** 15 g/kg/daily **(n=10)** | **Cohort 4** **30** µg/kg/daily (n= 8)*** |
| **Baseline** | | | | |
| **Mean (SD), cm/Year** | 3.6 (1.0) | 4.0 (2.3) | 4.0 (2.3) | 4.5 (1.2) |
| Median | 3.5 | 4.1 | 4.1 | 4.5 |
| **Post-Treatment** | | | | |
| **Mean, (SD), cm/year** | 5.9 (1.6) | 5.9 (0.9) | 6.1 (1.1) | 6.6 (1.2) |
| Median | 5.6 | 5.6 | 5.9 | 7.0 |
| **Change from Baseline** | | | | |
| **Mean (SD), cm/year** | **2.3 (1.9)** | **1.9 (2.0)** | **2.0 (2.0)** | **2.1 (2.1)** |
| **Nominal p-value*** | **0.002** | **0.02** | **0.01** | **0.03** |
| **Percent increase from Baseline** | **65 %** | **46 %** | **50 %** | **46 %** |
| **Based on means (%)** | | | | |

* 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
***8 children have non-missing annualized growth velocity at both baseline and 6 months.

**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 four dose cohort study, children were

treated with either 2.5 µg/kg/day, 7.5 µg/kg/ day, 15 µg/kg/ day or 30 µg/kg/ day, respectively. A total of 35 children with achondroplasia with an average age of 7.6 years were enrolled in the study. Based on the efficacy and safety profile observed, all children participating in the first two cohorts of the Phase 2 study, who remained in the study, were offered the higher dose of 15 µg/kg/day during the 18 month extension study. Children in the third (15 ug/kg/day) and fourth (30 ug/kg/day) cohorts will remain on their current dose during the extension study.

**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.

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. 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 timing and design 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.



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