# BioMarin Announces Cumulative Additional Height Gain of 9.0 cm over 54 months versus Natural History in Children with Achondroplasia Treated with Vosoritide in Phase 2 Study

**Company Plans to Provide Topline Phase 3 Data by Year End**
**Company Presents Data Confirming that the Phase 3 and Phase 2 Study Participants have Similar Baseline Parameters**

SAN RAFAEL, Calif., Nov. 14, 2019 /PRNewswire/ -- BioMarin Pharmaceutical Inc. (NASDAQ: BMRN) provided an update on its clinical program for vosoritide, an analog of C-type Natriuretic Peptide (CNP), in children with achondroplasia, the most common form of disproportionate short stature in humans, at its annual R&D Day. An ongoing, open-label, dose finding Phase 2 study of vosoritide for achondroplasia demonstrated over 54 months that children in cohort 3 (N=10) of the study, at a dose of 15 µg/kg/day, achieved a statistically significant ($p < 0.005$) cumulative additional mean height gain of 9.0 cm compared to children, matched for age and gender, in a new natural history achondroplasia dataset (N=619). 2.2 cm of this additional increase occurred in the last 12 months further informing our understanding of vosoritide's ongoing treatment impact.

"By matching individual study participants to an new natural history database that has approximately 13,000 data points related to height, we have additional information supportive of this investigational therapy demonstrating significant and sustained growth," said Hank Fuchs, M.D., President Worldwide Research and Development. "We are grateful to the children and their families for their participation in our ongoing clinical trials, as well as those who contributed their information to the natural history database. The new natural history data comparisons add important context to 54 months of sustained growth improvement observed to date, which in combination with our Phase 3 results, will form the basis for potential marketing applications."

In addition, BioMarin reaffirmed that it plans to provide top-line data from the randomized, placebo-controlled Phase 3 study by the end of the year.

**Phase 3 and Dose Finding Phase 2 Study Populations have Similar Baseline Parameters**

Baseline parameters of study participants in the Phase 3 study were compared to the baseline parameters of the Phase 2 study participants, illustrating the similarity between the studies.

| | **Phase II C3 (5-14 years eligible)** | **Phase III (5-18 years eligible) (Pooled, blinded data)** |
|---|---|---|
| Baseline AGV | 4.04cm/yr | 4.16cm/yr |
| Mean Age at Enrollment (range) | 8.0 (6-11) | 8.71 (5-14) |
| Male vs Female | 40.0% vs 60.0% | 52.9% vs 47.1% |

**Status Update on Vosoritide Ongoing Randomized, Placebo-Controlled Phase 2 Infants and Young Children Study**

In the global Phase 2 study in infants and young children up to age 5 with achondroplasia, enrollment of cohort 1 of 24 to 60 months is complete, and enrollment of cohort 2 of six- to 24-months is expected to be completed by the end of 2019. In the third cohort of newborns to six months old, all three open label sentinels have been enrolled in the study for safety observation prior to cohort expansion planned in December.

**Description of Phase 3 Study**

BioMarin expects top line results from the fully enrolled Phase 3 study of vosoritide in children by year end 2019. The global Phase 3 study is a randomized, placebo-controlled study of vosoritide in approximately 110 children with achondroplasia ages five to 14 for 52 weeks. The study will be followed by a subsequent open-label extension when all subjects receive active treatment. Children in this study will have completed a minimum six-month baseline study to determine their respective baseline growth velocity prior to entering the Phase 3 study. Vosoritide is being tested in children whose growth plates are still open. This is approximately 25% of people with achondroplasia. The primary endpoint of the study is the change in growth velocity from baseline over one year in children treated compared to placebo. The company also plans to augment the growth velocity data with assessments of proportionality and functionality.

**Description of Phase 2 Dose Finding Study**

The primary objectives of the open-label, sequential cohort, dose-finding study were to evaluate the safety and tolerability of daily subcutaneous vosoritide and to determine the dose to carry forward to Phase 3. Secondary objectives were to evaluate the effects of vosoritide on change from pre-treatment baseline in annualized growth velocity (cm/year), height Z-scores, and body segment proportionality, the vosoritide pharmacokinetic (PK) profile, and biomarkers of vosoritide activity, and endochondral ossification.

**Description of Phase 2 Study in Infants and Young Children Ages 0 to 5 Years**

The Phase 2 vosoritide study is a randomized, placebo-controlled study of vosoritide in approximately 70 infants and young children with achondroplasia, aged zero to less than 60 months, for a period of 52 weeks. The study will be followed by a subsequent open-label extension trial when all subjects receive active treatment. Children in this study will have completed a three-to-six month baseline study to determine their respective baseline growth prior to entering the Phase 2 study. The primary objectives of the study are to evaluate safety, tolerability, and the effect of vosoritide on height Z-scores, which is the number of standard deviations in relation to the mean height of age- and gender-matched, average stature children. The company also plans to augment the height Z-score data with assessments including proportionality, functionality, quality of life, sleep apnea, and foramen magnum dimension, as well as the advent of major illnesses and surgeries.

**Vosoritide Safety**

Vosoritide, administered in over 28,000 injections, was generally well tolerated at all doses. The majority of adverse events (AEs) were mild and no serious adverse events (SAEs) 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 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.

**About Achondroplasia**

Achondroplasia, the most common form of disproportionate short stature in humans, is characterized by slowing of endochondral ossification, which results in disproportionate short stature and disordered architecture in the long bones, spine, face and base of the skull. 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 the need for 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% of people with achondroplasia. In the U.S., Europe, Latin America and the Middle East, there are currently no licensed medicines for achondroplasia.

**About BioMarin**

BioMarin is a global biotechnology company that develops and commercializes innovative therapies for patients with serious and life-threatening rare and ultra-rare genetic diseases. The company's portfolio consists of seven commercialized products and multiple clinical and pre-clinical product candidates. For additional information, please visit www.biomarin.com. Information on such website is not incorporated by reference into this press release.

A full replay of the R&D Day presentation can be found at BioMarin.com.

**Forward-Looking Statement**

This press release contains forward-looking statements about the business prospects of BioMarin Pharmaceutical Inc. (BioMarin), including, without limitation, statements about: the development of BioMarin's vosoritide program generally; the potential benefits of vosoritide for infants and young children; the continued clinical development of vosoritide and the timing and conduct of such clinical program; the possible results of such studies; and BioMarin's expectation of top line results from the fully enrolled Phase 3 study of vosoritide in children by year end 2019. 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 enroll participants into such clinical trials, 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 other risks and uncertainties detailed from time to time under the caption "Risk Factors" and elsewhere in the BioMarin's Securities and Exchange Commission (SEC) filings, including, without limitation, BioMarin's Quarterly Report on Form 10-Q for the quarter ended September 30, 2019, and future SEC filings and reports by BioMarin. BioMarin undertakes no duty or obligation to update any forward-looking statements contained in this press release as a result of new information, future events or changes in its expectations.

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