BioMarin Announces New England Journal of Medicine Publishes Vosoritide Phase 2 Study Showing Sustained Annualized Growth Up to 42 Months in Children with Achondroplasia

Company Announces Enrollment Met for 2-5 Year-Old Cohort in Separate Phase 2 Study in Infants and Young Children

SAN RAFAEL, Calif., June 18, 2019 /PRNewswire/ -- BioMarin Pharmaceutical Inc. (NASDAQ:BMRN) announced that the *New England Journal of Medicine* (NEJM) published online today results from a Phase 2 dose-finding and extension study for vosoritide, an investigational analog of C-type Natriuretic Peptide (CNP), in children with achondroplasia. The data demonstrated that vosoritide was generally well tolerated with a mild side effect profile and resulted in a sustained increase in annualized growth velocity for up to 42 months in children aged 5 to14 years with achondroplasia, the most common form of disproportionate short stature in humans. The results will also appear in the July 4th printed issue.

In addition, the company announced that it had met its enrollment goal of the first cohort (n=30) of a separate Phase 2 study of vosoritide in infants and young children ages two to five years.

"Our research continues to investigate the potential of vosoritide to assist in skeletal growth in children with achondroplasia," said Ravi Savarirayan, M.B., B.S., M.D., lead author of the NEJM study and investigator from the Murdoch Children's Research Institute, Royal Children's Hospital, University of Melbourne, Parkville, Victoria, Australia. "I am hopeful that this ongoing clinical development program will be able to demonstrate a meaningful difference for children with achondroplasia."

The NEJM publication described results of an ongoing open-label, Phase 2 study in children with achondroplasia, where vosoritide demonstrated a sustained increase in height and associated height Z scores for up to 42 months of treatment in children in cohort 3 receiving a continuous dose of 15 µg/kg/day. Annualized growth velocity increased from baseline in all cohorts during each 12-month interval by 1.10 to 2.34 cm/year through 42 months. In cohort 3 (n=10) receiving 15 µg/kg continuous dosing from baseline, the mean annualized growth velocity derived between 30 and 42 months was 5.51 cm/year representing a 1.46 cm/year (95% CI −0.15, 3.07) change from baseline. In cohort 4 (n=9) receiving 30 µg/kg continuous dosing from baseline, the mean annualized growth velocity between 18 and 30 months was 5.60 cm/year representing a 1.10 cm/year (95% CI −0.27, 2.48) change from baseline.

"The results published today by NEJM demonstrate the importance of researching a therapeutic option that explicitly addresses the underlying cause of achondroplasia," said Hank Fuchs, M.D., President, Worldwide Research and Development at BioMarin. "The rapid completion of enrollment in the two to five year old cohort of our ongoing infant and toddler Phase 2 study is an important milestone for our clinical program. We are grateful to the children and their families for their participation in our ongoing clinical trials as we continue to investigate important and sustained outcomes for those with achondroplasia, as well as contribute to the body of scientific literature on achondroplasia."

Once-daily subcutaneous administration of vosoritide was associated with a side-effect profile that was generally mild. Injection-site reactions were mild and transient. Blood pressure and pulse rate were monitored

frequently after the initial dose was administered. All reductions in blood pressure from test to test were reported as non-serious and transient and resolved without medical intervention; none resulted in interruption or discontinuation of the study-drug regimen. Serious adverse events occurred in four children and included grade 3 obstructive sleep apnea, grade 1 tonsillar hypertrophy, grade 3 thyroglossal cyst, and grade 3 syrinx. No deaths occurred. No adverse events related to disproportionate skeletal growth or clinically significant adverse cardiovascular effects were observed. In addition, there were no reports of grade 3 or higher or serious hypersensitivity reactions.

Height Z-scores also continued to improve over 42 months and there was proportional growth between the upper and lower body segments. Standing height was converted to an age and sex appropriate Z-score by comparison with Centers for Disease Control and Prevention reference standards for average-height children. Dose-dependent increases in height Z-scores were observed in the children who received a dose of up to 15.0 µg/kg/day for 6 months; those who received a dose of 30.0 µg/kg/day had a similar increase. Vosoritide resulted in a sustained increase in height Z-score for up to 42 months; the mean increase from baseline to 42 months was 1.03±0.57 (95% CI 0.62, 1.43) in cohort 3; the mean increase from baseline to 30 months was 1.06±0.30 (95% CI 0.81, 1.31) in cohort 4. These improvements in Z-scores represent closure of approximately 15-20% of the "growth gap" of 5-6 SD between average-height and children with achondroplasia in 42 months.

Confidence intervals evaluating changes from baseline in annualized growth velocity, Z-scores, and upper-to-lower body segment ratio were considered descriptive and no adjustment for multiplicity was made.

Vosoritide has been granted orphan drug designation in both the United States and Europe.

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.

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 minimum three-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-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.

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 where 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.

Lifetime Impact Studies

BioMarin is conducting lifetime impact of achondroplasia studies in Europe (LIAISE) and Latin America (LISA) to contribute to the understanding of the impact of achondroplasia.

About Achondroplasia

Achondroplasia, the most common form of disproportionate short stature in humans, 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% 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.

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; the timing, design and conduct of the planned Phase 2 study in infants and young children and of other ongoing and possible future studies of vosoritide; the expected results of such studies, the ability to use the primary objectives of the Phase 2 study to support the use of vosoritide in infants and young children; BioMarin's expectation of top line results from the fully enrolled Phase 3 study of vosoritide in children by year end 2019 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 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 March 31, 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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