BioMarin Announces The Lancet Publishes Detailed Vosoritide Phase 3 Data Demonstrating Statistically Significant Increase in Annualized Growth Velocity (AGV) Over 52 Weeks in Children with Achondroplasia

Statistically Significant Increases in Height Z Score

Prespecified Subgroup Analysis Demonstrates Consistent AGV and Z Score increases Over Placebo

SAN RAFAEL, Calif., Sept. 8, 2020 /PRNewswire/ -- BioMarin Pharmaceutical Inc. (NASDAQ: BMRN) today announced that *The Lancet* has published online results from a randomized, double-blind, phase 3, placebo-controlled, multicenter trial for vosoritide, an investigational analog of C-type Natriuretic Peptide (CNP), in children aged 5 to 18 years with achondroplasia. Achondroplasia is the most common form of disproportionate short stature in humans. The data demonstrated that daily subcutaneous administration of vosoritide to children with achondroplasia resulted in significantly increased growth velocity and height Z scores over baseline after one year of treatment as compared to those who received placebo with similar adverse effect profiles.

"This study provides the first robust evidence for a precision therapy for achondroplasia that has the potential to fundamentally change the clinical management, growth trajectory, and treatment recommendations for affected children." said Ravi Savarirayan, M.B., B.S., M.D., lead author of The Lancet study and investigator from the Murdoch Children's Research Institute, Royal Children's Hospital, University of Melbourne, Parkville, Victoria, Australia. "As a treating physician, the lack of therapeutic options for children with achondroplasia represents an unmet medical need in this area."

The primary endpoint was change from baseline in AGV at 52 weeks in participants administered daily subcutaneous injections of vosoritide, at a dose of 15.0 µg/kg/day, compared with placebo. The findings demonstrated that the adjusted mean difference in AGV between children in the vosoritide group and placebo group was 1.57cm per year in favor of vosoritide (95% CI: 1.22 - 1.93, p value <0·0001), a substantial proportion of the approximately 2 cm/yr AGV deficit relative to average-stature children. The results of subgroup analyses for change from baseline in AGV were consistent with the overall mean difference between treatment groups in favor of vosoritide, with all 95% CIs overlapping.

"The consistency of the 54 months of data from an earlier Phase 2 study and this completed Phase 3 study over 12 months provides a strong data set on the clinical

benefits of vosoritide in children with achondroplasia," said Hank Fuchs, M.D., President, Worldwide Research and Development at BioMarin. "These data are part of a robust clinical program and lay the foundation for a potential first drug therapy to address the underlying molecular pathology in children with achondroplasia. We are looking forward to working with regulatory authorities to address this unmet medical need with a therapeutic choice that demonstrates a meaningful increase in skeletal growth."

Baseline AGV was calculated from the increase in standing height measured over the last six months of the run-in study. Post-baseline AGV was calculated from standing height at baseline and 52-weeks, and then summarized by treatment arm. As of October 30th, 2019, the 52-week placebo-controlled study was completed, and 119 participants had enrolled in the extension study, where all children are receiving vosoritide.

Secondary Endpoints, Height Z Score

A prespecified analysis of the secondary endpoint of change from baseline in height Z score, (which measures the height deficit in standard deviations relative to the mean forage- and gender-matched average stature children), was also performed. The findings demonstrated that the adjusted mean difference in height Z score change from baseline between children in the vosoritide group and placebo group was +0.28 in favor of vosoritide (95% CI: 0.17 – 0.39, p value <0.0001). The results of subgroup analyses were consistent and showed that all estimates of the mean difference between treatment groups were greater than or equal to zero and the 95% CIs were overlapping.

There were no adverse effects on, or significant improvements in upper to lower body segment proportionality in children receiving vosoritide during this 52-week study. As expected due to the duration of follow up, no statistically significant changes in secondary endpoints related to wider health outcomes such as quality of life, activities of daily living, and frequency and type of medical and surgical interventions were found. Either a longer treatment period or earlier treatment initiation will be required to detect these changes. As such, an ongoing, open-label, phase 3, extension study will continue to evaluate the balance of benefits and harms of vosoritide until the children reported in this study reach final adult height. This study will collect data regarding vosoritide therapy on wider health measures compared with registry data of untreated children with achondroplasia. This long-term study will also provide data on whether treatment of children with achondroplasia with vosoritide will result in a pubertal growth spurt, which appears to be absent in this condition, and provide the opportunity to detect any harms associated with long-term therapy.

In addition, a phase 2, randomized, double-blind, placebo-controlled trial of vosoritide in infants and younger children (aged 3 months to <60 months) with achondroplasia has been designed to provide further insights into the long-term treatment effects on body proportionality and growth, as well as how earlier treatment might affect the most substantial medical complications (e.g., foramen magnum stenosis with brainstem compression).

Safety Summary

Vosoritide, administered at 15.0 ug/kg/day in this Phase 3 randomized, double-blinded placebo-controlled study over one year, was generally well tolerated. The majority of adverse events (AEs) were mild and no serious adverse events were reported as study drug-related. Injection site reactions were the most common drug-related AEs, and all were transient. No clinically significant blood pressure decreases, or new safety findings were observed.

Regulatory Status

BioMarin announced that the European Medicines Agency (EMA) validated the Company's Marketing Authorization Application, as well as submitted a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) for vosoritide. Vosoritide has also received orphan drug designation from the FDA and EMA for the treatment of children with achondroplasia. The Orphan Drug Designation program is intended to advance the evaluation and development of products that demonstrate promise for the diagnosis and/or treatment of rare diseases or conditions.

Description of Phase 3 Study

The global Phase 3 study was a randomized, double-blind, placebo-controlled study of vosoritide in 121 children with achondroplasia aged 5 to 14 for 52 weeks. (The enrollment age criteria were 5 to 18 per the study protocol). Vosoritide is being tested in children whose growth plates are still open. This is approximately 25% of people with achondroplasia. Children in this study have completed a minimum six-month baseline study to determine their baseline growth velocity prior to entering the Phase 3 study. The primary endpoint of the study was the change in growth velocity from baseline over one year in children treated with vosoritide compared to placebo. Children in the study will continue to be evaluated in an ongoing open-label extension study where all study participants receive active treatment until the children participating in this study reach final adult height.

Description of Ongoing 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 participants 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 score. 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.

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 AGV (cm/year), height Z score, and body segment proportionality, the vosoritide pharmacokinetic (PK) profile, and biomarkers of vosoritide activity, and endochondral ossification. All children who completed the 24-month dose finding study were then eligible to continue long term follow up in the ongoing extension study which provides long term evidence of efficacy, durability of effect and safety.

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 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, the Middle East, and most of Asia Pacific, there are currently no approved medicines for achondroplasia.

About BioMarin

BioMarin is a global biotechnology company that develops and commercializes innovative therapies for serious and life-threatening rare and ultra-rare genetic diseases. The Company's portfolio consists of six commercialized products and multiple clinical and pre-clinical product candidates. For additional information, please visit www.biomarin.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. (BioMarin), including, without limitation, statements about: the development of BioMarin's vosoritide development program generally and specifically about the results of the phase 3 study, the consistency of Phase 2 and Phase 3 studies, the requirement of a longer treatment period or earlier treatment initiation to detect changes in secondary endpoints related to wider health outcomes such as quality of life, activities of daily living, and frequency and type of medical and surgical interventions, the expectation that the Phase 2 dose finding study will provide data on whether treatment of children with achondroplasia with vosoritide will result in a pubertal growth spurt and provide the opportunity to detect any harms associated with long term therapy, the continued clinical development of vosoritide and the timing and conduct of such clinical program; the possible results of such studies, and discussions with health authorities about marketing applications. 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: 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 June 30, 2020, 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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