BioMarin Announces Benefit Maintained for Over Two Years in Children with Achondroplasia Treated with Vosoritide in Phase 3 Extension Study

Children Treated with Vosoritide Demonstrate Cumulative Height Gain of 3.52 cm at Year 2 Compared to Untreated Children

No New Safety Signals Observed

Current Regulatory Review Timelines on Track

SAN RAFAEL, Calif., Dec. 21, 2020 /PRNewswire/ -- BioMarin Pharmaceutical Inc. (NASDAQ: BMRN) today announced that children in the open-label long-term extension of the Phase 3 study of vosoritide, an investigational, once daily injection analog of C-type Natriuretic Peptide (CNP), maintained an increase in Annual Growth Velocity (AGV) through the second year of continuous treatment. These analyses are the result of the combination of data of the same patients enrolled in three consecutive trials. In the first trial, a "run in" period consisted of longitudinal measurement of height in all patients prior to receiving treatment. After at least six months observation in the run-in trial, 121 patients were randomized 1:1 to receive either placebo or vosoritide at a dose of 15 ug/kg/day. One year later, patients previously receiving placebo were crossed over to receive vosoritide in an open-label treatment extension study, while those patients previously on vosoritide remained on treatment.

A first analysis, comparing all children randomized and treated with vosoritide for two years (n=52) to all children from the run-in study who were randomized to receive placebo with an untreated observation period of two years (n=38), showed improvement in one-year height change in the treated group relative to the untreated group that was similar in the second year of treatment, 1.79 cm, as in the first year of treatment, 1.73 cm. The cumulative height gain over the 2-year treatment period was 3.52 cm compared to untreated children, which is the sum of the first year (1.73) and the second year (1.79).

Yearly change in standing height (cm)	**Year 1**	**Year 2**
Untreated (N=38*), mean (SD)	3.96 (0.92)	3.82 (0.99)
Vosoritide (N=52), mean (SD)**	5.69 (0.97)	5.61 (1.09)
Treatment effect (95% CI)	1.73 (1.33 - 2.14)	1.79 (1.35 - 2.24)
P-value* **	<0.0001	<0.0001

*38 participants were enrolled in the run-in study more than 12 months and were at least 5 years of age at that point of time in advance of randomization and therefore contribute at least two years of evaluation of height in the absence of treatment.

**Data from 6 patients were unavailable due to patient withdrawals during Year 2 (n=2) and due to restrictions in study conduct because of Covid-19 (n=4). The patients whose data are not available due to Covid-19 are still on treatment.

*** p-value for unadjusted treatment effect.

A second supportive analysis evaluated the treatment effect of vosoritide administered continuously for over two years, including all children regardless of the duration of prior observation (N=119; 58 treated and 61 untreated children). This analysis showed a mean improvement in AGV in the vosoritide treated group of 1.69 cm/year, compared with untreated subjects, calculated over the entire observation period. A similar method was used in the analysis of the effect of one year's treatment with vosoritide previously published in The Lancet on Sept. 5, 2020, demonstrating a placebo-adjusted improvement in AGV of 1.57 cm/year. (Table 2 in Lancet publication, DOI: https://doi.org/10.1016/S0140-6736(20)31541-5).

In the vosoritide treated group, AGV declined by -0.14 cm/year during the second year of vosoritide treatment compared to the baseline AGV established in the 6 months prior to the first year of treatment. This decline is similar to the annual AGV decline with age that has been observed in natural history studies, as well as during one year of treatment with placebo (-0.12 cm/year), further supporting the maintenance of treatment effect.

Retention of subjects on treatment was high with 93% of patients originally randomized to receive vosoritide remaining on treatment two years later.

Vosoritide was generally well tolerated with no new safety concerns. Serious adverse events observed in the trial were representative of common childhood illnesses and were deemed unrelated to vosoritide. No new safety findings have emerged, and clinically inconsequential blood pressure changes were mild, transient and self-limiting.

"BioMarin is committed to the long-term follow up of children participating in vosoritide studies and the overall health of people with achondroplasia. We look forward to sharing more data on wider health measures that either require a longer treatment period or starting treatment at a younger age. We are also specifically studying the impact of

vosoritide in infants at risk of serious and potentially fatal medical complications related to achondroplasia," said Hank Fuchs, M.D., President Worldwide Research and Development at BioMarin. "We are grateful for the support of the children and their families who are in these studies, the clinical trial investigators and their staffs, BioMarin employees, and the community. We look forward to sharing more detailed information at an upcoming medical meeting and further contributing to the scientific body of knowledge about vosoritide and its potential impact over time."

"Follow up data from extension studies are critical to expanding our understanding of the wider impact of achondroplasia," said Melita Irving, Clinical Geneticist at Guy's and St Thomas' NHS Foundation Trust, London, UK and investigator for the vosoritide clinical program at the Evelina London Children's Hospital. "BioMarin has developed a comprehensive clinical program designed to address the effects on health and day to day living by evaluating proportionality, functionality, quality of life, sleep apnea, and foramen magnum dimension."

Vosoritide Safety

The 2-year data demonstrated that vosoritide, administered at 15ug/kg/day was generally well tolerated with no new safety findings. 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's marketing applications for vosoritide are currently under review by both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), and if approved would be the first therapy for achondroplasia in the U.S. and Europe. The FDA's Prescription Drug User Fee Act target action date is August 20, 2021. The Committee for Medicinal Products for Human Use (CHMP) opinion is expected in Europe in the second half of 2021.

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.

Robust Clinical Program

Description of Phase 3 Extension Study

This is an ongoing open-label long-term extension study to a completed pivotal, double-blind, placebo-controlled study of vosoritide in children with achondroplasia. A total of 119 children were enrolled in the extension study after completion of the pivotal phase 3 study and are receiving open-label treatment with vosoritide 15 mcg/kg daily. Vosoritide is being tested in children whose growth plates are still "open." This is approximately 25% of people with achondroplasia. The extension study is evaluating safety, AGV, and cumulative annual height gain until participants reach final adult height. A wide range of secondary and exploratory endpoints include anthropometric measures such as height Z-score, body and limb proportionality and joint geometry; biochemical, biomarker and radiological assessments of bone growth and health; and evaluations of health-related quality of life (HRQoL), developmental status, and functional independence. These additional endpoints address the overall impact vosoritide has on achondroplasia.

Description of Phase 2 Study for Children at Risk of Life-Threatening Foramen Magnum Compression

This is a Phase 2 randomized, controlled, open-label clinical trial with an open-label extension to investigate the safety of vosoritide in infants with achondroplasia at risk of requiring cervicomedullary decompression surgery to alleviate compression at the foramen magnum, the opening in the base of the skull through which the spinal cord passes. In addition, the study will also measure a secondary endpoint to evaluate the effect of vosoritide on growth of the foramen magnum volume through MRI scans. Within a month of study initiation in November, two of the planned 20 (10%) participants enrolled.

Foramen magnum compression is the foremost life-threatening complication of achondroplasia in infants. This study investigates the safety of vosoritide in infants aged 0 -1 years of age with achondroplasia who have evidence of foramen magnum compression at-risk for requiring cervicomedullary decompression surgery. Those infants are under close observation for the appearance of neurological signs of progressive foramen magnum compression, and the current standard of care is palliative with many eventually requiring surgery. The study aims to enroll approximately 20 infants, who will be randomized to either current standard of care plus vosoritide treatment or current standard of care alone for a two-year period. After the two-year randomized period, children in the study would be eligible to receive vosoritide in an open-label, 3-year additional extension period. The study will examine the incidence of adverse events between the two groups, volume MRI measurements of the foramen magnum, skull and

spine, and progression to requiring decompression surgery.

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

This is a Phase 2 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. Currently, cohorts 1 and 2 are fully enrolled and cohort 3 is 85% (17/20) enrolled. The remaining study participants to enroll are in the observational period and are expected to be dosed in 1Q 2021.

About Achondroplasia

Achondroplasia, the most common form of skeletal dysplasia leading to 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 change 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 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 six 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 development program generally and specifically about the results of the extension of the Phase 3 trial, the maintenance of AGV after two years, the similarity of AGV and height gain in the first and second years of the Phase 3 study, the similarity of AGV and height gain to earlier studies, the continued clinical development of vosoritide and the timing and conduct of such clinical program; the enrollment expectations for ongoing clinical trials; the possible results of such studies, the timing of decisions by health authorities about marketing applications, and the Company's plans to discuss provision of the two-year data with health 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: final analysis of the extension of the Phase 3 data, 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 record data during a global pandemic, 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, 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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