BioMarin Highlights Key Milestones for 2019 at 37th Annual J.P. Morgan Healthcare Conference in San Francisco

Completed Enrollment of Subject Cohort to Support BLA Submission Through Accelerated Approval (AA) Pathway for Valoctocogene Roxaparvovec Gene Therapy for Hemophilia A
Phase 3 Vosoritide Data in Children with Achondroplasia Expected Year End 2019
CHMP Opinion for Palynziq® (pegvaliase) Injection for Patients 16 and older with PKU Anticipated in 1Q 2019 and Potential Approval in EU in 2Q 2019

SAN RAFAEL, Calif., Jan. 7, 2019 /PRNewswire/ -- BioMarin Pharmaceutical Inc. (NASDAQ: BMRN), a company focused on innovative therapies to treat rare diseases, provided highlights to the investment community on its key milestones for 2019 at the 37th Annual J.P. Morgan Healthcare Conference in San Francisco.

"With multiple development and regulatory milestones expected in 2019, BioMarin maintains strong pipeline momentum. We are looking forward to advancing multiple product candidates in parallel through the development process," said Jean-Jacques Bienaimé, BioMarin Chairman and CEO. "Our focus on the unmet needs in rare genetic diseases and demonstrating meaningful clinical benefits provides the foundation to move rapidly through product development and commercialization."

During the company's presentation at the conference, Bienaimé provided information on the company's development program for valoctocogene roxaparvovec gene therapy for severe hemophilia A. BioMarin has completed enrollment of the initial cohort of patients in its Phase 3 program intended to support a BLA submission through the accelerated approval pathway. A decision to submit a BLA through an accelerated approval pathway is tracking for the second half of 2019. If the company submits a BLA using the accelerated approval pathway, it will disclose additional information on the timing of its plans regarding the BLA submission. The complete Phase 3 study is targeting enrollment of 130 patients by mid-year 2019.

Valoctocogene roxaparvovec has Orphan Drug designation from the FDA and the European Medicines Agency (EMA). Valoctocogene roxaparvovec has also been accepted for Priority Medicines (PRIME) scheme from the EMA. Additionally, the FDA has granted valoctocogene roxaparvovec Breakthrough Therapy designation.

BioMarin also 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.

BioMarin expects top line results from the fully enrolled Phase 3 study of vosoritide in children by year end 2019. The Phase 2 study in infants and young children up to age 5 with achondroplasia study enrollment is on track, and in this early part of the study, vosoritide is generally well-tolerated. See "About Vosoritide Phase 3 Study" and "About Vosoritide Phase 2 Infant and Young Children Study" below for more information on the studies.

Vosoritide has been granted orphan drug designation in both the U.S. and Europe.

In addition, Bienaimé noted during the presentation that the company is anticipating an opinion from the Committee for Medicinal Products for Human Use (CHMP), the scientific committee of the European Medicines Agency (EMA) on Palynziq® (pegvaliase) Injection for the treatment of patients 16 and older with PKU in 1Q 2019. If the CHMP provides a positive opinion in 1Q 2019, then in 2Q 2019, it is possible that the European Commission (EC) could provide marketing authorization in the European Union. In addition, the company provided 2019 global revenue guidance for Palynziq of between $70 and $100 million.

Palynziq, a PEGylated recombinant phenylalanine ammonia lyase enzyme approved in the United States in May 2018, is the first approved enzyme substitution therapy to target the underlying cause of phenylketonuria (PKU) by helping the body to break down Phe. PKU is a rare genetic disease that manifests at birth and results in a variety of cumulative toxic effects on the brain. Palynziq is BioMarin's second approved treatment for this serious condition. In March 2018, the European Medicines Agency accepted BioMarin's submission of a Marketing Authorization Application for Palynziq.

Gene Therapy Manufacturing

BioMarin has constructed one of the largest gene therapy manufacturing facilities of its kind, which is located in Novato, California. Good Manufacturing Practices (GMP) production of valoctocogene roxaparvovec has commenced supporting clinical development activities and will support any anticipated commercial demand. This facility is capable of supporting approximately 4,000 doses per year, and the production process was developed in accordance with International Conference on Harmonisation guidance for Pharmaceuticals for Human Use to facilitate worldwide registration with health authorities. Clinical supplies for valoctocogene roxaparvovec for Hemophilia A and BMN 307, a pre-clinical gene therapy for PKU, are produced in this facility.

About BioMarin and Disease Information

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.

About Hemophilia A

Hemophilia A, also called factor VIII (FVIII) deficiency or classic hemophilia, is a genetic disorder caused by missing or defective factor VIII, a clotting protein. Although it can be passed down from parents to children, about 1/3 of cases are caused by a spontaneous mutation, a new mutation that was not inherited. Approximately 1 in 10,000 people predominantly male is born with Hemophilia A. People living with the disease are not able to form blood clots efficiently and are at risk for excessive bleeding from modest injuries, potentially endangering their lives. People with severe hemophilia often bleed spontaneously into their muscles or joints. The standard of care for the 49% of individuals with hemophilia A who are severely affected is a prophylactic regimen of Factor VIII infusions two to three times per week. Even with prophylactic regimens, many people still experience spontaneous bleeding events that result in progressive and debilitating joint damage.

Valoctocogene Roxaparvovec Phase 1/2 Study Safety

Overall, valoctocogene roxaparvovec has been well-tolerated by patients across all doses. No patients developed inhibitors to Factor VIII and no patients withdrew from the study. The most common AEs across all dose cohorts were alanine aminotransferase (ALT) elevation (11 patients, 73%); arthralgia, aspartate aminotransferase elevation, and headache (7 patients each, 47%); back pain and fatigue (5 patients each, 33%). Two patients reported SAEs during the study. One patient was hospitalized for observation after developing Grade 2 pyrexia with myalgia and headache within 24 hours of receiving valoctocogene roxaparvovec. The event resolved within 48 hours following treatment with paracetamol, an over-the-counter treatment for pain and fever. The event was assessed as related to valoctocogene roxaparvovec. The other AE was assessed as not related to the therapy, attributed to a planned knee surgery to treat hemophilic arthropathy, and Grade 1 in severity. No complications were reported.

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 is currently no licensed medicines for achondroplasia.

About Vosoritide Phase 3 Study

The global Phase 3 study is a randomized, placebo-controlled study of vosoritide in approximately 110 children with achondroplasia ages 5-14 for 52 weeks. The study will be followed by a subsequent open-label extension. 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.

About Vosoritide Phase 2 Infant and Young Children Study

The Phase 2 vosoritide study is a randomized, placebo-controlled study of vosoritide in approximately 70 infants and young children with achondroplasia ages zero to less than 60 months for 52 weeks. The study will be followed by a subsequent open-label extension. 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.

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 Phenylketonuria

PKU, or PAH deficiency, is a genetic disorder affecting approximately 90,000 diagnosed patients in the regions of the world where BioMarin operates and is caused by a deficiency of the enzyme PAH. This enzyme is required for the metabolism of Phe, an essential amino acid found in most protein-containing foods. If the active enzyme is not present in sufficient quantities, Phe accumulates to abnormally high levels in the blood and becomes toxic to the brain, resulting in a variety of complications including severe intellectual disability, seizures, tremors, behavioral problems and psychiatric symptoms. As a result of newborn screening efforts implemented in the 1960s and early 1970s, virtually all individuals with PKU under the age of 40 in countries with newborn screening programs are diagnosed at birth and treatment is implemented soon after. PKU can be managed with a Phe-restricted diet, which is supplemented by low-protein modified foods and Phe-free medical foods; however, the strict diet is difficult for most adult patients to adhere to the extent needed for achieving adequate control of blood Phe levels.

To learn more about PKU and PAH deficiency, please visit www.PKU.com. Information on such website is not incorporated by reference into this press release.

About Palynziq

Palynziq substitutes the deficient phenylalanine hydroxylase (PAH) enzyme in PKU with the PEGylated version of the enzyme phenylalanine ammonia lyase to break down Phe. Palynziq is administered using a dosing regimen designed to facilitate tolerability; Palynziq's safety profile consists primarily of immune-mediated responses, including anaphylaxis, for which robust risk management measures effective in clinical trials are in place.

The dosing and administration of Palynziq follows an induction, titration, and maintenance paradigm. Treatment is individualized to the lowest effective and tolerated dosage. Prescribers may consider increasing to a maximum of 40 mg once daily in patients who have not achieved a response with 20 mg once daily for at least 24 weeks. Prescribers are instructed to discontinue treatment in patients who have not responded after 16 weeks of continuous treatment with the maximum dosage of 40 mg once daily. Periodic blood Phe monitoring is recommended, and patients should be counseled on how to adjust their dietary intake, as needed, based on blood Phe concentrations.

Indication

Palynziq (pegvaliase-pqpz) Injection is a phenylalanine-metabolizing enzyme indicated to reduce blood phenylalanine concentrations in adult patients with PKUwho have uncontrolled blood phenylalanine concentrations greater than 600 µmol/L on existing management.

Important Safety Information

BOXED WARNING: RISK OF ANAPHYLAXIS

- **Anaphylaxis has been reported after administration of PALYNZIQ and may occur at any time during treatment with PALYNZIQ.**
- **Administer the initial dose of PALYNZIQ under the supervision of a healthcare provider equipped to manage anaphylaxis, and closely observe patients for at least 60 minutes following injection. Prior to self-injection, confirm patient competency with self-administration, and patient's and observer's (if applicable) ability to recognize signs and symptoms of anaphylaxis and to administer auto-injectable epinephrine, if needed.**
- **Prescribe auto-injectable epinephrine to all patients treated with PALYNZIQ. Prior to the first dose, instruct the patient and observer (if applicable) on its appropriate use. Instruct the patient to seek immediate medical care upon its use. Instruct patients to carry auto-injectable epinephrine with them at all times during treatment with PALYNZIQ.**
- **PALYNZIQ is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the PALYNZIQ REMS.** Further information, including a list of qualified pharmacies, is available at www.PALYNZIQREMS.com (site will be live within 24 hours) or by telephone 1-855-758-REMS (1-855-758-7367).

WARNINGS AND PRECAUTIONS

Anaphylaxis

- Signs and symptoms of anaphylaxis reported include syncope, hypotension, hypoxia, dyspnea, wheezing, chest discomfort/chest tightness, tachycardia, angioedema (swelling of face, lips, eyes, tongue), throat tightness, skin flushing, rash, urticaria, pruritus, and gastrointestinal symptoms (vomiting, nausea, diarrhea).
- Anaphylaxis generally occurred within 1 hour after injection; however, delayed episodes occurred up to 48 hours after PALYNZIQ administration.
- Consider having an adult observer for patients who may need assistance in recognizing and managing anaphylaxis during treatment with PALYNZIQ. If an adult observer is needed, the observer should be present during and for at least 60 minutes after administration of PALYNZIQ, and should be able to administer auto-injectable epinephrine and call for emergency medical support upon its use
- Anaphylaxis requires immediate treatment with auto-injectable epinephrine. Prescribe auto-injectable epinephrine to all patients receiving PALYNZIQ and instruct patients to carry auto-injectable epinephrine with them at all times during treatment with PALYNZIQ. Prior to the first dose, instruct the patient and observer (if applicable) on how to recognize the signs and symptoms of anaphylaxis, on how to properly administer auto-injectable epinephrine, and to seek immediate medical care upon its use. Consider the risks associated with auto-injectable epinephrine use when prescribing Palynziq. Refer to the auto-injectable epinephrine prescribing information for complete information.
- Consider the risks and benefits of readministering PALYNZIQ following an episode of anaphylaxis. If the decision is made to readminister PALYNZIQ, administer the first dose under the supervision of a healthcare provider equipped to manage anaphylaxis and closely observe the patient for at least 60 minutes following the dose. Subsequent dose titration of PALYNZIQ should be based on patient tolerability and therapeutic response.
- Consider premedication with an H_1-receptor antagonist, H_2-receptor antagonist, and/or antipyretic prior to administration of PALYNZIQ based upon individual patient tolerability.

Other hypersensitivity reactions

- Hypersensitivity reactions other than anaphylaxis have been reported in 196 of 285 (69%) patients treated with PALYNZIQ.
- Consider premedication with an H_1-receptor antagonist, and/or antipyretic prior to PALYNZIQ administration based upon individual patient tolerability.
- Management of hypersensitivity reactions should be based on the severity of the reaction, recurrence of the reaction, and the clinical judgment of the healthcare provider, and may include dosage adjustment, temporary drug interruption, drug discontinuation, or treatment with antihistamines, antipyretics, and/or corticosteroids.

ADVERSE REACTIONS

- The most common adverse reactions (at least 20% of patients in either treatment phase) were injection site reactions, arthralgia, hypersensitivity reactions, headache, generalized skin reaction lasting at least 14 days, pruritus, nausea, abdominal pain, oropharyngeal pain, vomiting, cough, diarrhea, and fatigue.
- Of the 285 patients exposed to PALYNZIQ in an induction/titration/maintenance regimen in clinical trials, 31 (11%) patients discontinued treatment due to adverse reactions. The most common adverse reactions leading to treatment discontinuation were hypersensitivity reactions (6% of patients)—including anaphylaxis (3% of patients) and angioedema (1% of patients)—arthralgia (4% of patients), generalized skin reactions lasting at least 14 days (2% of patients), and injection site reactions (1% of patients)
- The most common adverse reactions leading to dosage reduction were arthralgia (14% of patients), hypersensitivity reactions (9% of patients), injection site reactions (4% of patients), alopecia (3% of patients), and generalized skin reactions lasting at least 14 days (2% of patients)
- The most common adverse reactions leading to temporary drug interruption were arthralgia (13% of patients), hypersensitivity reactions (13% of patients), anaphylaxis (4% of patients), and injection site reactions (4% of patients)

Blood Phenylalanine Monitoring and Diet

- Obtain blood phenylalanine concentrations every 4 weeks until a maintenance dosage is established.
- After a maintenance dosage is established, periodically monitor blood phenylalanine concentrations.
- Counsel patients to monitor dietary protein and phenylalanine intake, and adjust as directed by their healthcare provider.

DRUG INTERACTIONS

Effect of PALYNZIQ on other PEGylated products

- In a single dose study of PALYNZIQ in adult patients with PKU, 2 patients receiving concomitant injections

of medroxyprogesterone acetate suspension (a formulation containing PEG 3350) experienced hypersensitivity reactions, and 1 of the 2 patients also experienced anaphylaxis.
- The clinical effects of concomitant treatment with different PEGylated products is unknown. Monitor patients treated with PALYNZIQ and concomitantly with other PEGylated products for hypersensitivity reactions.

USE IN SPECIFIC POPULATIONS

Pregnancy and Lactation

- PALYNZIQ may cause fetal harm when administered to a pregnant woman.
- If PALYNZIQ is administered during pregnancy, or if a patient becomes pregnant while receiving PALYNZIQ or within 1 month following the last dose of PALYNZIQ, healthcare providers should report PALYNZIQ exposure by calling 1-866-906-6100.
- Monitor blood phenylalanine concentrations in breastfeeding women treated with PALYNZIQ.

Pediatric use

- The safety and efficacy of PALYNZIQ in pediatric patients have not been established.

Geriatric Use

- Clinical studies of PALYNZIQ did not include patients aged 65 years and older.

You are encouraged to report side effects to report suspected adverse events to BioMarin at 1-877-695-8826 and the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**.**

Please see full Prescribing Information, including Boxed Warning, at PALYNZIQ.com/hcp, which will be available in 24 hours.

Forward Looking Statement

This press release contains forward-looking statements about the business prospects of BioMarin Pharmaceutical Inc., including, without limitation, statements about its development programs and regulatory actions related to these programs, including the timing of (i) decisions by regulators, including the EMA's decision regarding BioMarin's MAA for Palynziq, (ii) BioMarin's global revenue guidance for Palyzniq in 2019 (iii) BioMarin's preclinical studies and clinical studies and trials, (iv) completion of enrollment of those studies and trials, and (v) announcements of data from those studies and trials; the production capacity of BioMarin's gene therapy manufacturing facility; the continued clinical development and commercialization of BioMarin's commercial products and product candidates, including BioMarin's plans to complete the Phase 3 study enrollment of valoctocogene roxaparvovec by mid-year 2019 and potentially decide in the second half of 2019 whether to submit a BLA for valoctocogene roxaparvovec for accelerated approval and the possible approval and commercialization of BioMarin's product candidates. 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 our product candidates, the continued clinical experiences of the patients in the current clinical studies; the content and timing of decisions by the FDA, the European Commission and other regulatory authorities; our ability to successfully manufacture our product candidates for the preclinical and clinical trials; and those factors detailed in BioMarin's filings with the Securities and Exchange Commission (SEC), including, without limitation, the factors contained under the caption "Risk Factors" in BioMarin's Quarterly Report on Form 10-Q for the quarter ended September 30, 2018 as such factors may be updated by any subsequent reports. 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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