BioMarin, Pioneer in Phenylketonuria, to Begin Clinical Trial with BMN 307 Gene Therapy

Health Authorities in the U.S. and U.K. Clear Path to Start of Clinical Trial, Patients Expected to be Dosed in Q1 2020 with Commercial Scale Material
Potential 3rd Therapy to treat Phenylketonuria from Leader in PKU Therapies and 2nd Gene Therapy in Company's Clinical Pipeline
Gene Therapy Manufacturing Productivity More Than Doubles Potential Capacity Up to 10,000 Gene Therapy Doses Annually, Depending on Dose and Product Mix

SAN RAFAEL, Calif., Jan. 13, 2020 /PRNewswire/ -- BioMarin Pharmaceutical Inc. (NASDAQ: BMRN), a pioneer in treatments for the rare disease Phenylketonuria (PKU) and in gene therapy clinical research, announced today that both the U.S. Food and Drug Administration (FDA) and the Medicines and Healthcare Products Regulatory Agency (MHRA) in the U.K. have granted the Company Investigational New Drug (IND) status and approved its Clinical Trial Application (CTA), respectively, for its investigational gene therapy candidate BMN 307. BMN 307 is an AAV5-phenylalanine hydroxylase (PAH) gene therapy designed to normalize blood phenylalanine (Phe) concentration levels in patients with PKU. BMN 307 will be evaluated to determine whether a single dose of treatment can restore natural Phe metabolism, normalize plasma Phe levels, and enable a normal diet in patients with PKU.

The Company expects to start dosing patients in PHEARLESS, a Phase 1/2 study, in the first quarter of 2020 with product made at commercial scale from its award-winning gene therapy manufacturing facility. The Company is actively preparing regulatory submissions to open additional clinical sites in other countries. BMN 307 represents a potential third PKU treatment option from BioMarin and its second gene therapy clinical program. Both the FDA and European Medicines Agency have granted BMN 307 Orphan Status.

BMN 307 follows BioMarin's first investigational gene therapy clinical program: valoctocogene roxaparvovec to treat severe hemophilia A, currently in Phase 3. Based on data from an interim analysis of the ongoing Phase 3 study, the European Medicines Agency validated a Marketing Authorization Application in the EU for valoctocogene roxaparvovec, and the review process has begun. The Company also has submitted a Biologics License Application to the FDA and anticipates the review to begin in February 2020.

"With BMN 307, we are joining together our expertise in PKU biology and the knowledge we have gained from developing the only two approved therapies for PKU with our understanding of gene therapy clinical development and manufacturing from our valoctocogene roxaparvovec experience," said Hank Fuchs, President, Worldwide Research and Development at BioMarin. "BioMarin has stood with the PKU community for over 15 years and remains dedicated to continuing to increase the body of medical knowledge in this devastating disease."

PKU is a rare genetic disease that manifests at birth and is marked by an inability to break down Phe, an amino acid that is commonly found in many foods. Left untreated, high levels of Phe become toxic to the brain and may lead to serious neurological and neuropsychological issues, affecting the way a person thinks, feels, and acts. Due to the seriousness of these symptoms, in many countries infants are screened at birth to ensure early diagnosis and treatment to avoid intellectual disability and other complications. According to treatment guidelines, PKU patients should maintain lifelong control of their Phe levels.

BMN 307 Clinical Program

BioMarin's clinical program is composed of two key studies. PHEARLESS, a Phase 1/2 study, will evaluate the safety, efficacy, and tolerability of a single intravenous administration of BMN 307 in patients with PKU. The study consists of a dose-escalation phase, followed by a cohort expansion phase once an initially efficacious dose has been demonstrated. In addition, BioMarin is sponsoring an observational study, PHENOM, which has already started enrolling patients with PKU to measure both established and new markers of disease and clinical outcomes over time.

BioMarin's 15-Plus Year Commitment to PKU Research

For more than 15 years, BioMarin has been a pioneer in ongoing research to help improve the lives of PKU patients. BioMarin has treated approximately 7,000 PKU patients around the world. The company has two approved PKU therapies, and the investigational gene therapy BMN 307 is currently in development. BioMarin has conducted 40 clinical studies in PKU and has sponsored 38 external clinical studies. BioMarin researchers

have authored 54 publications in medical and scientific journals on PKU and supported another 52 publications by external researchers.

About Gene Therapy

Gene therapy is a form of treatment designed to address a genetic problem by adding a normal copy of the defective gene. The functional gene is inserted into a vector containing a small DNA sequence that acts as a delivery mechanism, providing the ability to deliver the functional gene to targeted cells. The cells can then use the information from the normal gene to build the functional proteins that the body needs, potentially reducing or eliminating the cause of the disease.

Gene Therapy Manufacturing

BioMarin has leveraged its knowledge and experience in manufacturing complex biological products to design, construct and validate a state-of-the-art vector production facility in Novato, California. This facility is the site of production for both valoctocogene roxaparvovec and BMN 307. Manufacturing capabilities are an essential driver for our gene therapy programs and allows us to control quality, capacity, costs and scheduling enabling rapid development. Manufacture of BMN 307 was performed with a commercial ready process at scale in this facility. Production of BMN 307 with a commercial ready process at scale reduces risk associated with making process changes later in development and will speed overall development timelines significantly.

Ongoing process development efforts and experience gained at commercial scale have led to improvements in productivity and operational efficiency. The ability to scale out the facility with additional equipment combined with the improvements in productivity result in a doubling of overall potential capacity to 10,000 doses per year, combined for both products, depending on final dose and product mix. This improvement in productivity is anticipated to meet both commercial and clinical demand for both valoctocogene roxaparvovec and BMN 307 well in to the future.

About Phenylketonuria

PKU, or PAH deficiency, is a genetic disorder affecting approximately 50,000 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, it is difficult for most patients to adhere to the life-long strict diet to the extent needed to achieve adequate control of blood Phe levels. Dietary control of Phe in childhood can prevent major developmental neurological toxicities, but poor control of Phe in adolescence and adulthood is associated with a range of neurocognitive disabilities with significant functional impact.

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

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 BMN 307 program generally, BioMarin's planned submissions to regulatory authorities for BMN 307, BioMarin's gene therapy manufacturing capabilities, the impact of using material manufactured at commercial scale in a clinical trial, the timing and results of BioMarin's planned Phase 1/2 trial of BMN 307, and the review of marketing applications for valoctocogene roxaparvovec. 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 BMN 307; the content and timing of decisions by the U.S. Food and Drug Administration, the

European Commission and other regulatory authorities; uncertainties inherent in research and development, including unfavorable new clinical data and additional analyses of existing clinical data; the results and timing of current and future clinical trials related to BMN 307; our ability to reproducibly and consistently manufacture sufficient quantities of BMN 307, the possibility that changes may be required to the current manufacturing process; 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, 2019 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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