U.S. FDA Placed a Clinical Hold on BMN 307 Phearless Phase 1/2 Gene Therapy Study in Adults with PKU Based on Interim Pre-clinical Study Findings

BioMarin Also Pausing Further Enrollment of Additional Participants Outside the U.S. in Phearless Phase 1/2 Study

BioMarin is Working with FDA and Other Health Authorities and Will Communicate Next Steps When Available

SAN RAFAEL, Calif., Sept. 6, 2021 /PRNewswire/ -- BioMarin Pharmaceutical Inc. (NASDAQ: BMRN) announced today that the U.S Food and Drug Administration (FDA) placed a clinical hold on the BMN 307 Phearless Phase 1/2 study. The Phearless study is evaluating BMN 307, an investigational AAV5-phenylalanine hydroxylase (PAH) gene therapy, in adults with phenylketonuria (PKU). The FDA's clinical hold was based on interim safety findings from a pre-clinical, non-GLP pharmacology study.

The Company carried out this pre-clinical study to understand the durability of BMN 307 activity in mice bearing two germline mutations, which may predispose the mice to the development of malignancy. One mutation eliminated the PAH gene that's missing in PKU and the second rendered the animals immunodeficient. Of 63 animals treated, six of seven animals administered BMN 307 at the highest dose group (2e14 Vg/kg) had tumors on liver necropsy 52 weeks after dosing with evidence for integration of portions of AAV vector into the genome. No lesions were observed in any mice at 24 weeks. Five of these animals had adenomas and one had a hepatocellular carcinoma (HCC). The translatability of these findings to humans is uncertain and under further investigation.

To date, the Company has only dosed humans in the Phearless Phase 1/2 clinical study with lower doses of either 2e13 vg/kg or 6e13 vg/kg. Due in part to the risk previously identified by historical rodent studies, the liver health of Phearless study participants is regularly monitored. The Company will work with the Data Review Board and Principal Investigators to further evaluate the study participants who have been dosed and will continue to monitor them over the long-term. The clinical significance of these pre-clinical rodent findings has not been established and cancers due to AAV integration have not been observed in larger animals or humans. BioMarin is pausing further enrollment into this global Phase 1/2 study until the investigation of these findings is completed. The company is working with the FDA and other health authorities and will communicate next steps for the program when available.

"More than 3,000 patients have been treated with gene therapy, and there are no reports of cancers emerging as a consequence. Acknowledging the complexity of the issue as highlighted in this week's FDA discussion, integrational mutagenesis and resultant cancer formation has been observed in mice using other AAV vectors," said Hank Fuchs, M.D., President, Worldwide Research and Development at BioMarin. "Therefore, we plan to investigate these findings. For patients who have already received lower doses of these vectors, we will continue to carefully evaluate and monitor their health. We are committed to understand and mitigate any risk of cancer causation."

About Phenylketonuria

PKU, or phenylalanine hydroxylase (PAH) deficiency, is a genetic disorder affecting approximately 70,000 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 severe 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 Company pausing enrollment globally in the Phearless Phase 1/2 study, the impact of the pre-clinical findings on the 307 clinical program, the predictability of the pre-clinical findings on human patients, the development of BioMarin's BMN 307 program generally, including the impact on the timing and process for regulatory interactions and decisions. 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: 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, the outcome of ongoing review of clinical and pre-clinical data; the outcome of additional experiments related to the preclinical findings; the results and timing of current and future clinical trials related to BMN 307; 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 June 30, 2021 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.

Contacts:

Investors	Media
Traci McCarty	*Debra Charlesworth*
BioMarin Pharmaceutical Inc.	*BioMarin Pharmaceutical Inc.*
(415) 455-7558	*(415) 455-7451*

SOURCE BioMarin Pharmaceutical Inc.

https://investors.biomarin.com/2021-09-06-U-S-FDA-Placed-a-Clinical-Hold-on-BMN-307-Phearless-Phase-1-2-Gene-Therapy-Study-in-Adults-with-PKU-Based-on-Interim-Pre-clinical-Study-Findings