BioMarin Plans Regulatory Submissions for Marketing Authorization of Valoctocogene Roxaparvovec to Treat Severe Hemophilia A in 4Q 2019 in both U.S. and Europe

Potential 1st Marketing Application for a Gene Therapy Product in Any Type of Hemophilia to be Reviewed by Health Authorities
Late-Breaking Abstract at the 27th International Society on Thrombosis and Haemostasis (ISTH) 2019 Congress Presents 3 Years of Efficacy and Safety of Valoctocogene Roxaparvovec

SAN RAFAEL, Calif., July 8, 2019 /PRNewswire/ -- BioMarin Pharmaceutical Inc. (NASDAQ: BMRN) announced today that based on recent meetings with health authorities in the U.S. and Europe, the company plans to submit marketing applications to both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in 4Q 2019 for its investigational gene therapy, valoctocogene roxaparvovec, for adults with severe hemophilia A. These submissions will be based on the updated three-year Phase 1/2 data and the recently completed Phase 3 interim analysis of patients treated with material from the to-be-commercialized process. Both submissions are expected to represent the first time a gene therapy product for any type of hemophilia will be reviewed for marketing authorization by health authorities.

Both the FDA and EMA continue to prioritize interactions related to the review of valoctocogene roxaparvovec through the Breakthrough Therapy Designation program in the U.S and the Priority Medicines (PRIME) regulatory initiative in Europe. Valoctocogene roxaparvovec is one of the first therapies to go through the new PRIME initiative. FDA and EMA grant expedited review designations for investigational therapies that address unmet medical needs in the treatment of a serious condition and/or show the potential to offer major therapeutic advantages over existing treatments.

"People with severe hemophilia A continue to experience clinically relevant breakthrough bleeds despite the current standard of care and can be limited in their physical activities," said Professor John Pasi, M.B., Ch.B., Ph.D., from Barts and the London School of Medicine and Dentistry; the chief investigator for the valoctocogene roxaparvovec Phase 1/2 study and a principal investigator for the Phase 3 study. "Valoctocogene roxaparvovec represents a potentially transformative investigative therapy that could improve patients' quality of life, including consequences of bleeding, physical functioning, role functioning, emotional impact, treatment concern, and worry."

"We applaud the FDA's efforts to incorporate the patient voice in the regulatory review process. Powerful and moving testimonials from clinical study participants have helped serve as a critical element in the FDA's considerations of potentially the first commercially available gene therapy for any type of hemophilia," said Hank Fuchs, M.D., President, Global Research and Development at BioMarin. "As important, we commend the EMA PRIME initiative for enabling enhanced interactions and early dialogue that have optimized our development plans and have helped speed up evaluation of this novel investigational gene therapy."

ISTH Late-Breaking Abstract

Earlier today, Professor Pasi presented data in a late-breaking abstract session on the efficacy and safety of valoctocogene roxaparvovec in an ongoing Phase 1/2 study at the 27th International Society on Thrombosis and Haemostasis (ISTH) 2019 Congress in Melbourne, Australia.

The three-year update of the 6e13 vg/kg dose cohort in the Phase 1/2 study demonstrated that bleed rate control and reduction in Factor VIII usage was maintained for a third year following a single administration of valoctocogene roxaparvovec. In the year prior to study entry, the mean Annualized Bleed Rate (ABR) was 16.3 and the median was 16.5. Over three years, the ABR was reduced to a mean of 0.6 and a median of zero. This represents a 96% reduction in participants' mean ABR, and there is 100% resolution of target joints. There was also a 96% reduction in participants' mean annualized Factor VIII usage rate over three years, and all participants remain off Factor VIII prophylaxis. Factor VIII levels sustained over a three-year period were sufficient to achieve striking hemostatic efficacy. Factor VIII expression has entered a plateau phase where the rate of decline has substantially slowed, which could be indicative of durable, long-term expression.

"We are grateful to the study participants, who have made this progress possible in less than four years since the first participant was enrolled in a clinical study," Fuchs added. "We have been moving efficiently through the development process, in no small part because of our ability to treat clinical trial participants with valoctocogene roxaparvovec produced using our commercial process. Utilization of to-be-commercialized material during Phase 3 studies significantly de-risks the program, as no production or facility changes need to be made to support commercial demand."

Valoctocogene Roxaparvovec Safety Summary

Overall, valoctocogene roxaparvovec continues to have a favorable safety profile and has been well-tolerated by participants across all doses in the Phase 1/2 and Phase 3 studies. No participants developed inhibitors to Factor VIII, and no participants withdrew from the study. All participants have remained off Factor VIII prophylaxis. Corticosteroid use was transient with no long-lasting clinical sequelae. No participants have developed thrombotic events. Transient liver biomarker abnormalities and infusion-associated reactions have been the primary treatment-related adverse events, with no emergence of any delayed adverse events.

GENEr8-1 To Complete Enrollment in Early Fall 2019

While the planned regulatory submissions in 4Q 2019 will be based on an interim analysis of the Phase 3 GENEr8-1 study results, the trial will continue to enroll to its planned completion target of 130 total patients. Completion of this portion of the study is not required for initial marketing authorizations of valoctocogene roxaparvovec. The final analysis from the Phase 3 GENEr8-1 study will be the basis for evaluating the clinical superiority of valoctocogene roxaparvovec to prophylactic Factor VIII replacement therapy. The completion of enrollment of the GENEr8-1 study is expected in the early fall of 2019.

Regulatory Status

The FDA granted valoctocogene roxaparvovec Breakthrough Therapy Designation based on preliminary clinical evidence indicating that valoctocogene roxaparvovec may demonstrate substantial improvement over available therapy. The FDA's Breakthrough Therapy Designation program is intended to facilitate and expedite development and review of new drugs to address unmet medical need in the treatment of a serious condition. The EMA has granted access to its Priority Medicines (PRIME) regulatory initiative for valoctocogene roxaparvovec for its potential to benefit patients with unmet medical needs based on early clinical data.

BioMarin's valoctocogene roxaparvovec has also received orphan drug designation from the FDA and EMA for the treatment of severe hemophilia A. 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.

Gene Therapy Manufacturing

BioMarin has constructed, commissioned, and validated one of the first gene therapy manufacturing facilities of its kind in the world, which is located in Novato, California. Marketing authorization documentation will be included in the filings, and the facility is ready for inspection to support approval. This facility can support 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, facilitating worldwide registration with health authorities. In 2018, the International Society for Pharmaceutical Engineering (ISPE) selected the Company's gene therapy manufacturing facility as the Facility of the Year Category Winner for Project Execution.

About Hemophilia A

People living with hemophilia A lack enough Factor VIII protein to help their blood clot and are at risk for painful and/or potentially life-threatening bleeds from even modest injuries. Additionally, people with severe hemophilia A often experience painful, spontaneous bleeds into their muscles or joints. Individuals with hemophilia A diagnosed as severe make up 43 percent of the hemophilia A population. The standard of care for severe hemophilia A is a prophylactic regimen of replacement Factor VIII infusions administered intravenously up to two to three times per week. Despite these regimens, many people continue to experience bleeds, resulting in progressive and debilitating joint damage, which can have a major impact on their quality of life.

Hemophilia A, also called Factor VIII deficiency or classic hemophilia, is an X-linked genetic disorder caused by missing or defective Factor VIII, a clotting protein. Although it is 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 is born with Hemophilia A.

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 seven 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 development of BioMarin's valoctocogene roxaparvovec program generally; the company's plans for regulatory submissions in the U.S, and Europe in 4Q 2019, expectations regarding the company's ongoing clinical trials, and the completion of enrollment of the Phase 3 study. 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 valoctocogene roxaparvovec, including final analysis of the above interim data; additional data from the continuation of the Phase 1/2 trial and the Phase 3 trial, any potential adverse events observed in the continuing monitoring of the participants in the clinical trials; the content and timing of decisions by the U.S. Food and Drug Administration, the European Commission and other regulatory authorities; the content and timing of decisions by local and central ethics committees regarding the clinical trials; our ability to successfully manufacture valoctocogene roxaparvovec for the clinical trials and commercially, if approved; and those other risks detailed from time to time under the caption "Risk Factors" and elsewhere in BioMarin's Securities and Exchange Commission (SEC) filings, including BioMarin's Quarterly Report on Form 10-Q for the quarter ended March 31, 2019, and future 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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