BioMarin Resubmits Biologics License Application (BLA) for Valoctocogene Roxaparvovec AAV Gene Therapy for Severe Hemophilia A to the FDA

BLA Includes Substantial Body of Data from Pivotal Phase 3 and Ongoing Phase 1/2 Studies

If Approved, Would Be 1st Gene Therapy in U.S. for Treatment of Severe Hemophilia A

SAN RAFAEL, Calif., Sept. 29, 2022 /PRNewswire/ -- BioMarin Pharmaceutical Inc. (NASDAQ: BMRN) announced today that the Company resubmitted a Biologics License Application (BLA) to the U.S. Food and Drug Administration (FDA) for its investigational AAV gene therapy, valoctocogene roxaparvovec, for adults with severe hemophilia A. The resubmission incorporates the Company's response to the FDA Complete Response (CR) Letter for valoctocogene roxaparvovec gene therapy issued on August 18, 2020, and subsequent feedback, including two-year outcomes from the global GENEr8-1 Phase 3 study and supportive data from five years of follow-up from the ongoing Phase 1/2 dose escalation study.

BioMarin anticipates an FDA response by the end of October on whether the BLA resubmission is complete and acceptable for review. Typically, BLA resubmissions are followed by a six-month review procedure. However, the Company anticipates three additional months of review may be necessary based on the number of data read-outs that will emerge during the procedure. If approved, valoctocogene roxaparvovec would be the first commercially-available gene therapy in the U.S. for the treatment of severe hemophilia A.

The FDA granted Regenerative Medicine Advanced Therapy (RMAT) designation to valoctocogene roxaparvovec in March 2021. RMAT is an expedited program intended to facilitate development and review of regenerative medicine therapies, such as valoctocogene roxaparvovec, that are expected to address an unmet medical need in patients with serious conditions. The RMAT designation is complementary to Breakthrough Therapy Designation, which the Company received for valoctocogene roxaparvovec in 2017.

In addition to the RMAT Designation and Breakthrough Therapy Designation, BioMarin's valoctocogene roxaparvovec also received orphan drug designation from the EMA and FDA for the treatment of severe hemophilia A. Orphan drug designation is reserved for

medicines treating rare, life-threatening or chronically debilitating diseases. The European Commission (EC) granted conditional marketing authorization to valoctocogene roxaparvovec gene therapy under the brand name ROCTAVIAN™ on August 24, 2022 and endorsed the recommendation from the European Medicines Agency (EMA) to maintain orphan drug designation, thereby granting a 10-year period of market exclusivity in the European Union.

"We are pleased to reach this point in the development program for valoctocogene roxaparvovec and look forward to working with the FDA with the goal of bringing a potentially transformative therapy to people with severe hemophilia A in the United States," said Hank Fuchs, M.D., President of Worldwide Research and Development at BioMarin. "This large and robust data set provided in this BLA resubmission shows an encouraging efficacy profile. We remain committed to sharing these data with the public, along with even longer-term data generated through our ongoing clinical trials and any post-approval studies, to further our understanding of AAV gene therapy in severe hemophilia A and of gene therapies more broadly."

The resubmission includes a substantial body of data from the valoctocogene roxaparvovec clinical development program, the most extensively studied gene therapy for severe hemophilia A, including two-year outcomes from the global GENEr8-1 Phase 3 study. The GENEr8-1 Phase 3 study demonstrated stable and durable bleed control, including a reduction in the mean annualized bleeding rate (ABR) and the mean annualized Factor VIII infusion rate. In addition, the data package included supportive evidence from five years of follow-up from the 6e13 vg/kg dose cohort in the ongoing Phase 1/2 dose escalation study. The resubmission also includes a proposed long-term extension study following all clinical trial participants for up to 15 years, as well as two post-approval registry studies.

Robust Clinical Program

BioMarin has multiple clinical studies underway in its comprehensive gene therapy program for the treatment of severe hemophilia A. In addition to the global Phase 3 study GENEr8-1 and the ongoing Phase 1/2 dose escalation study, the Company is also conducting a Phase 3, single arm, open-label study to evaluate the efficacy and safety of valoctocogene roxaparvovec at a dose of 6e13 vg/kg with prophylactic corticosteroids in people with severe hemophilia A (Study 270-303). Also ongoing are a Phase 1/2 Study with the 6e13 vg/kg dose of valoctocogene roxaparvovec in people with severe hemophilia A with pre-existing AAV5 antibodies (Study 270-203) and a Phase 1/2 Study with the 6e13 vg/kg dose of valoctocogene roxaparvovec in people with severe hemophilia A with active or prior Factor VIII inhibitors (Study 270-205).

Safety Summary

Overall, to date, a single 6e13 vg/kg dose of valoctocogene roxaparvovec has been well tolerated with no delayed-onset treatment related adverse events. The most common adverse events (AE) associated with valoctocogene roxaparvovec have occurred early and included transient infusion associated reactions and mild to moderate rise in liver enzymes with no long-lasting clinical sequelae. Alanine aminotransferase (ALT) elevation, a laboratory test of liver function, has remained the most common adverse drug reaction. Other adverse reactions have included aspartate aminotransferase (AST) elevation (101 participants, 63%), nausea (55 participants, 34%), headache (54 participants, 34%), and fatigue (44 participants, 28%). No participants have developed inhibitors to Factor VIII, thromboembolic events or malignancy associated with valoctocogene roxaparvovec.

About Hemophilia A

People living with hemophilia A lack sufficient functioning 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 the most severe form of hemophilia A (Factor VIII levels <1%) often experience painful, spontaneous bleeds into their muscles or joints. Individuals with the most severe form of hemophilia A make up approximately 50 percent of the hemophilia A population. People with hemophilia A with moderate (Factor VIII 1-5%) or mild (Factor VIII 5-40%) disease show a much-reduced propensity to bleed. Individuals with severe hemophilia A are treated with a prophylactic regimen of intravenous Factor VIII infusions administered 2-3 times per week (100-150 infusions per year) or a bispecific monoclonal antibody that mimics the activity of Factor VIII administered 1-4 times per month (12-48 injections or shots per year). Despite these regimens, many people continue to experience breakthrough 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 have hemophilia A.

About BioMarin

BioMarin is a global biotechnology company that develops and commercializes innovative therapies for people with serious and life-threatening genetic diseases and medical conditions. The Company selects product candidates for diseases and conditions that

represent a significant unmet medical need, have well-understood biology and provide an opportunity to be first-to-market or offer a significant benefit over existing products. The Company's portfolio consists of eight commercial products and multiple clinical and preclinical product candidates for the treatment of various diseases. For additional information, please visit www.biomarin.com.

Forward-Looking Statements

This press release contains forward-looking statements about the business prospects of BioMarin Pharmaceutical Inc. (BioMarin), including without limitation, statements about: BioMarin anticipating an FDA response by the end of October on whether the BLA resubmission is complete and acceptable for review, BioMarin's expectations regarding the duration of the review procedure, valoctocogene roxaparvovec being the first commercially-available gene therapy in the U.S. for the treatment of severe hemophilia A, if approved, BioMarin's commitment to sharing longer-term data generated through its ongoing clinical trials and any post-approval studies. 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 results and timing of current and planned preclinical studies and clinical trials of valoctocogene roxaparvovec; additional data from the continuation of the clinical trials of valoctocogene roxaparvovec, any potential adverse events observed in the continuing monitoring of the participants in the clinical trials; the content and timing of decisions by the FDA and other regulatory authorities, including decisions to grant additional marketing registrations based on an EMA license; 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; and those 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, 2022 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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