BioMarin Announces Publication in New England Journal of Medicine of One-Year Results from Phase 3 Pivotal Trial with Valoctocogene Roxaparvovec Gene Therapy in Adults with Severe Hemophilia A

New England Journal of Medicine Publishes Editorial: Prepare the Way for Hemophilia A Gene Therapy

Significantly Reduced Bleeding and Factor VIII Utilization Compared to Baseline Factor VIII Prophylactic Therapy

Mean Annualized Bleeding Rate (ABR) Reduced by 84% (p-value <0.001)

Mean Annualized Factor VIII Utilization Rate Reduced by 99% (p-value <0.001)

SAN RAFAEL, Calif., March 17, 2022 /PRNewswire/ -- BioMarin Pharmaceutical Inc. (NASDAQ: BMRN) today announced publication of results from the Phase 3 GENEr8-1 study of valoctocogene roxaparvovec, an investigational gene therapy for the treatment of adults with severe hemophilia A, in the *New England Journal of Medicine* (NEJM). The article titled, "Valoctocogene Roxaparvovec Gene Therapy for Hemophilia A," reports one year or more of follow-up data from the study and is referenced in an editorial published in the same issue of the Journal acknowledging the potential benefit of zero bleeds and avoiding the use of prophylactic therapy.

The original research article reports that following a single infusion of valoctocogene roxaparvovec participants experienced substantially reduced annualized bleeding rates, reduced factor VIII utilization, and increased factor VIII activity, than they did in the year prior to study enrollment. In the pre-specified rollover population consisting of 112 participants enrolled from a prospective noninterventional study, mean annualized factor VIII concentrate use and mean treated bleeding rates after week 4 decreased post-infusion by 99% and 84%, respectively (both $P<0.001$). Overall, 121/134 (90%) participants had either no treated bleeds or fewer treated bleeds after infusion, compared with factor VIII prophylaxis as documented in the noninterventional study. At weeks 49–52, 88% of participants had median factor VIII activity of 5 IU/dL or higher, as measured using the chromogenic substrate (CS) assay.

"Breakthrough bleeding represents a high burden of disease management and an unmet medical need for many people. I am encouraged that during the first year of treatment,

90% of study participants had either zero treated bleeds or fewer treated bleeds post-infusion than with factor VIII prophylaxis," said Margareth C. Ozelo, MD, PhD, Director, Hemocentro UNICAMP, University of Campinas and Lead Principal Investigator of the GENEr8-1 Study. "These results reflect the potential for sustained hemostatic bleed control with this gene therapy for hemophilia A."

"We are proud to be pioneers in the study of gene therapy for severe hemophilia A and to share individual patient data that facilitates a more complete understanding of the full data set of this potentially transformative medicine," said Hank Fuchs, M.D., President of Worldwide Research and Development at BioMarin. "Valoctocogene roxaparvovec has been studied longer than any other gene therapy for hemophilia A, and year after year, we continue to increase our knowledge of how this investigational therapy may potentially benefit the lives of people with hemophilia A. We are grateful to the study participants and investigators for their essential role in this development program, which includes GENEr8-1, the largest gene therapy study in hemophilia A."

Valoctocogene Roxaparvovec Safety

This is the most current safety information from a two-year analysis of the Phase 3 GENEr8-1 study and covers overall safety of valoctocogene roxaparvovec. The safety included in the NEJM publication is based on a one-year analysis. All participants in the Phase 3 study received a single 6e13 vg/kg dose. No participants developed inhibitors to Factor VIII, malignancy, or thromboembolic events. During year two, no new safety signals emerged, and no treatment-related serious adverse events (SAE) were reported. Most patients had discontinued any corticosteroid (CS) use in year one, and there were no CS-related SAEs in the remaining patients being tapered off CS in year two. Overall, the most common adverse events (AE) associated with valoctocogene roxaparvovec 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 (119 participants, 89%), a laboratory test of liver function, remained the most common AE. Other common adverse events were headache (55 participants, 41%), arthralgia (53 participants, 40%), nausea (51 participants, 38%), aspartate aminotransferase (AST) elevation (47 participants, 35%), and fatigue (40 participants, 30%). In a Phase 1/2 study, an SAE of a salivary gland mass was identified in one study participant, who was treated more than five years ago, and was reported as unrelated to valoctocogene roxaparvovec by the investigator. The relevant health authorities were notified in late 2021, and all studies remain ongoing without modification. The independent Data Monitoring Committee (DMC) further reviewed the case. A genomic analysis is being conducted as prespecified in the clinical trial protocol.

GENEr8-1 Study Description

The global Phase 3 GENEr8-1 study is a single-arm, open-label study evaluating the efficacy and safety of valoctocogene roxaparvovec in people with severe hemophilia A (FVIII ≤ 1 IU/dL) who had been treated continuously with prophylactic exogenous factor VIII for a minimum of one year prior to enrollment. The primary efficacy endpoint was change from baseline in factor VIII activity (CS assay) at weeks 49–52 after infusion. Secondary efficacy endpoints included change from baseline in annualized use of factor VIII concentrate and annualized number of bleeding episodes after week 4. Safety was assessed through recording of adverse events, laboratory testing, and physical examination. Overall, a total of 134 participants received one valoctocogene roxaparvovec infusion at a dose of 6e13 vg/kg, and all participants had a minimum of 12 months of follow-up at the time of the data cut. The first 22 participants were directly enrolled into the Phase 3 study, 17 of whom were HIV-negative and dosed at least 2 years prior to the data cut date. The remaining 112 participants (rollover population) completed at least six months in a separate non-interventional study to prospectively assess bleeding episodes, factor VIII use, and health-related quality of life while receiving factor VIII prophylaxis prior to rolling over and receiving a single infusion of valoctocogene roxaparvovec in the GENEr8-1 study.

About Hemophilia A

Hemophilia A, also called factor VIII deficiency or hemophilia, is an X-linked genetic disorder caused by missing or defective factor VIII, a clotting protein. Although it is most-commonly 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.

People with the most severe form of hemophilia A often experience painful, spontaneous bleeds into their muscles or joints. Individuals with severe hemophilia A (FVIII levels <1%) make up approximately 45 to 50 percent of the hemophilia A population. People with hemophilia A with moderate (FVIII 1–5%) or mild (FVIII 5–40%) disease show a much-reduced propensity to bleed. The standard of care for adults with severe hemophilia A is a prophylactic regimen of replacement factor VIII infusions administered intravenously up to two to three times per week, or 100 to 150 infusions 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.

About BioMarin

BioMarin is a global biotechnology company that develops and commercializes innovative therapies for serious and life-threatening 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 Statements

This press release contains forward-looking statements about the business prospects of BioMarin Pharmaceutical Inc., including without limitation, statements about the potential benefit of zero bleeds and avoiding prophylactic use, the potential for sustained hemostatic bleed control with valoctocogene roxaparvovec, and how the therapy may benefit the lives of people with hemophilia A. 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 data and additional data from the continuation of these trials; any potential adverse events observed in the continuing monitoring of the patients in the clinical trials; the content and timing of decisions by the FDA, the EMA 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 Annual and quarterly Reports on Forms 10-K and 10-Q, 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.

Contacts:

Investors

Traci McCarty

BioMarin Pharmaceutical Inc.

(415) 455-

Media

Debra Charlesworth

BioMarin Pharmaceutical Inc.

7558 *(415) 455-7451*

SOURCE BioMarin Pharmaceutical Inc.

---

https://investors.biomarin.com/2022-03-17-BioMarin-Announces-Publication-in-New-England-Journal-of-Medicine-of-One-Year-Results-from-Phase-3-Pivotal-Trial-with-Valoctocogene-Roxaparvovec-Gene-Therapy-in-Adults-with-Severe-Hemophilia-A