BioMarin InvestorRoom

New England Journal of Medicine Published Open-label Study Showing Brineura® (cerliponase alfa) Reduced the Rate of Clinical Decline of Children with CLN2 Disease, a Form of Batten Disease

Less decline in motor and language function compared to historical controls

SAN RAFAEL, Calif., April 24, 2018 /PRNewswire/ -- BioMarin Pharmaceutical Inc. (NASDAQ: BMRN) today announced that the *New England Journal of Medicine* (NEJM) published updated results from a multi-center, open-label, dose-escalation and ongoing extension study evaluating the efficacy and safety of Brineura® (cerliponase alfa) in children with CLN2 disease in the May 2018 issue. The new data demonstrated that treatment with Brineura resulted in less decline in motor and language function compared to historical controls.

Brineura was approved in April 2017 by the U.S. Food and Drug Administration (FDA) to slow the loss of ambulation in symptomatic pediatric patients 3 years of age and older with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), also known as tripeptidyl peptidase 1 (TPP1) deficiency. Brineura also was approved in June 2017 by the European Commission. Brineura is the first treatment approved to treat children with CLN2 disease, a form of Batten disease.

The data published in NEJM showed that patients treated with Brineura experienced a slower rate of decline in motor and language function than historical controls (the unadjusted mean rate of decline in the score on the motor–language scale was 0.27±0.35 points per 48 weeks among the 23 treated patients as compared with 2.12±0.98 among the 42 historical controls, a difference of 1.85±0.21 points (95% CI, 1.51 to 2.18; P<0.001).

"To finally have a treatment for CLN2 available is an important step forward in advancing the standard of care for the children affected by this form of Batten disease," said Angela Schulz, M.D., lead author of the NEJM article and lead study investigator from the Department of Paediatrics, Children's Hospital, University Medical Center Hamburg-Eppendorf, Germany. "My hope in sharing this data in the New England Journal of Medicine is to increase awareness in the medical community of this ultra-rare disease and accelerate the time to diagnosis."

In addition to its publication in NEJM, Dr. Emily de los Reyes, M.D., director of the Batten Disease Center of Excellence at Nationwide Children's Hospital in Columbus, Ohio and a clinical trial investigator involved in the study, presented an updated analysis of the study at 96 weeks, at the invitation of the AAN Science Committee during the Clinical Trials Plenary Session at its 70th annual meeting on April 24th, 2018.

"CLN2 disease is a devastating and rapidly progressing condition that robs children of their motor function, including language and mobility. With the administration of cerliponase alfa, we see a reduction in that loss, which is of paramount importance to a child and their families where every day of sustained function is critical," said de los Reyes. "We appreciate the opportunity to share our findings with the larger community of healthcare providers, and to contribute to the knowledge that can further advance the standard of care in CLN2 and be useful in developing treatments for other forms of Batten disease."

The primary endpoint of the study—the time to a 2-point decline in motor-language score (range 0-6, 0 representing no function and 3 representing normal function for each of the two domains) assessed as mean change per 48 weeks compared to 42 historical controls—was met. Median time to a 2-point decline in motor-language score was 345 days (49.3 weeks) for natural history and not reached for treated patients (9 percent of treated patients had declined by 2 points at 345 days).

"With CLN2 disease, we are in a constant race against time. Brineura has the potential to change the course of this devastating disease. We continue to study the impact of Brineura and add to the body of scientific knowledge about CLN2," said Hank Fuchs, M.D., President, Worldwide Research and Development at BioMarin. "Our hope is that the Brineura data published and presented today ultimately benefits the children and families affected by CLN2."

Brineura is the first and only therapy approved by the U.S. Food and Drug Administration and European Union to treat children with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), a form of Batten disease also known as tripeptidyl peptidase 1 (TPP1) deficiency. Due to the rapidly progressing nature of the disease and clinical efficacy of its phase 1/2 study, Brineura was approved in just four years from first patient dosed to registration approval.

Study Design
An open-label study was conducted from September 2013 to November 2015 at five centers (Germany, Italy, US, and two in the UK) to assess the efficacy and safety of intraventricular cerliponase alfa in children with CLN2 disease. The studies were performed in accordance with the Declaration of Helsinki; the study protocol was approved by relevant ethics boards.

Eligible patients were aged 3-16 years of age with a diagnosis of CLN2 disease and a combined score of 3-6 on the motor and language domains of a CLN2 clinical rating scale (total range 0-6, 0 representing no function and 3 representing normal function for each of the two domains). Patients who completed the 48 week open-label study were eligible to enroll in a 240-week extension study of 300 mg administered every two weeks. Data from the extension study through November 1, 2016 were included in the findings published today. Patients enrolled in the NCL natural history database and diagnosed with CLN2 disease served as the comparison group.

About CLN2 Disease
Children with CLN2 disease typically begin experiencing seizures between the ages of 2 and 4 years old, preceded in the majority of cases by language development delay. The disease progresses rapidly with most affected children losing the ability to walk and talk by approximately 6 years of age. Initial symptoms are followed by movement disorders, motor deterioration, dementia, blindness, and death usually occurring between the ages of 8 and 12 years of age. During the later stages of the disease, feeding and tending to everyday needs become very difficult. BioMarin estimates the incidence of CLN2 disease is approximately one in 200,000 with up to 1,200 to 1,600 children in the regions of the world where BioMarin operates, many of whom are undiagnosed.

The neuronal ceroid lipofuscinoses (NCLs) are a heterogeneous group of lysosomal storage disorders that includes the autosomal recessive neurodegenerative disorder CLN2 disease. CLN2 disease is caused by mutations in the TPP1 gene resulting in deficient activity of the enzyme tripeptidyl peptidase 1 (TPP1). In the absence of TPP1, lysosomal storage materials normally metabolized by this enzyme accumulate in many organs, particularly in the brain and retina. Buildup of these storage materials in the cells of the nervous system contribute to the progressive and relentless neurodegeneration which manifests as loss of cognitive, motor, and visual functions.

About Brineura®
Brineura is a recombinant form of human tripeptidyl peptidase 1 (TPP1), the enzyme deficient in patients with CLN2 disease. It is an enzyme replacement therapy designed to restore TPP1 enzyme activity and break down the storage materials that cause CLN2 disease. In order to reach the cells of the brain and central nervous system, the treatment is delivered directly into the fluid surrounding the brain (cerebrospinal fluid) using BioMarin's patented technology.

For additional information regarding this product, please contact BioMarin Medical Information at medinfo@bmrn.com.

Indication
Brineura® (cerliponase alfa) is a prescription medication used to slow loss of ability to walk or crawl (ambulation) in symptomatic pediatric patients 3 years of age and older with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), also known as tripeptidyl peptidase 1 (TPP1) deficiency.

Important Safety Information
Brineura is a prescription medicine. Before treatment with Brineura, it is important to discuss your child's medical history with their doctor. Tell the doctor if they are sick or taking any medication and if they are allergic to any medicines. Your child's doctor will decide if Brineura is right for them. If you have questions or would like more information about Brineura, contact your child's doctor.

Brineura is only given by infusion into the fluid of the brain (known as an intraventricular injection) and using sterile technique to reduce the risk of infection. An intraventricular access device or port must be in place at least 5 to 7 days prior to the first infusion. Intraventricular access device-related infections were observed with Brineura treatment. If any signs of infection occur, contact your child's doctor immediately. Your child's intraventricular access device may need to be replaced over time.

Brineura should not be used in patients with active intraventricular access device-related complications (e.g., leakage, device failure, or device-related infection) and with shunts used to drain extra fluid around the brain.

Low blood pressure and/or slow heart rate may occur during and following the Brineura infusion. Contact your child's doctor immediately if these reactions occur.

Undesirable or hypersensitivity reactions related to Brineura treatment, including fever, vomiting, and irritability, may occur during treatment and as late as 24 hours after infusion. Your child may receive medication such as antihistamines before Brineura infusions to reduce the risk of reactions. Serious and severe allergic reactions (anaphylaxis) may occur. If a reaction occurs, the infusion will be stopped and your child may be given additional medication. If a severe reaction occurs, the infusion will be stopped and your child will receive appropriate medical treatment. If any signs of anaphylaxis occur, immediately seek medical care.

Safety and effectiveness in pediatric patients below 3 years of age have not been established.

The most common side effects reported during Brineura infusions included fever, problems with the electrical activity of the heart, decreased or increased protein in the fluid of the brain, vomiting, seizures, hypersensitivity, collection of blood outside of blood vessels (hematoma), headache, irritability, and increased white blood cell count in the fluid of the brain, device-related infection, slow heart rate, feeling jittery, and low blood pressure. Intraventricular device-related side effects included infection, delivery system-related complications, and increased white blood cell count in fluid of the brain. These are not all of the possible side effects with Brineura. Talk to your child's doctor if they have any

symptoms that bother them or that do not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Please see accompanying full Prescribing Information, or visit www.Brineura.com.

About BioMarin
BioMarin is a global biotechnology company that develops and commercializes innovative therapies for people with serious and life-threatening rare disorders. The company's portfolio consists of six commercialized products and multiple clinical and pre-clinical product candidates.

For additional information, please visit www.BMRN.com.

Forward Looking Statement

This press release contains forward-looking statements about the business prospects of BioMarin Pharmaceutical Inc. (BioMarin), including, without limitation, statements about: BioMarin's product Brineura, and specifically about expectations regarding its potential to change the course of CLN2 disease. 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 continued clinical development and commercialization of BioMarin's commercial products and product candidates; actions by regulatory authorities, our ability to manufacture sufficient quantities of Brineura for commercial use; and those factors detailed in BioMarin's filings with the Securities and Exchange Commission, including, without limitation, the factors contained under the caption "Risk Factors" and elsewhere in the Company's Securities and Exchange Commission (SEC) filings, including the Company's Annual Report on Form 10-K for the year ended December 31, 2017, 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 to update or alter any forward-looking statement, whether as a result of new information, future events or otherwise.

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