BioMarin InvestorRoom

FDA Approves Brineura™ (cerliponase alfa) for the Treatment of CLN2 Disease, a Form of Batten Disease and Ultra-Rare Pediatric Brain Disorder in Children

Brineura™ is the first FDA-approved treatment for this fatal neurodegenerative condition
BioMarin offers no cost genetic testing program to find the genetic cause of epilepsy
Conference Call and Web-cast to be Held Thursday, April 27 at 4:05 pm ET

SAN RAFAEL, Calif., April 27, 2017 /PRNewswire/ -- BioMarin Pharmaceutical Inc. (Nasdaq:BMRN) today announced that the U.S. Food and Drug Administration (FDA) approved Brineura™ (cerliponase alfa) 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 is the first treatment approved to treat children with CLN2 disease, a form of Batten disease.

CLN2 disease is an ultra-rare, rapidly progressive fatal brain condition, which affects less than one in one million U.S. residents, many of whom are undiagnosed. Every year approximately 20 children are born in the U.S. with CLN2 disease. These affected children completely lose the ability to walk and talk around 6 years of age. During the later stages of the disease, feeding and tending to everyday needs become very difficult with death often occurring between 8 and 12 years of age.

In clinical trials, Brineura, an enzyme replacement therapy, was shown to slow the loss of ambulation in symptomatic pediatric patients 3 years of age and older with CLN2 disease. It is the first enzyme replacement therapy to be directly administered to the brain, treating the underlying cause of the condition by replacing the deficient TPP1 enzyme. Using an established technique most often used in oncology – intraventricular administration– the therapy is delivered directly into fluid surrounding the brain, known as the cerebrospinal fluid.

To support the community of families with children with neurologic disorders, BioMarin in partnership with a commercial lab is offering a no cost genetic testing program called 'Behind the Seizure' to support early testing for children who experience seizures. In addition, BioMarin is investing in tools and resources to educate physicians on CLN2 disease in order to help them diagnose patients with this disease earlier and prevent them from being misdiagnosed during critical years when therapy could help slow the loss of ambulation.

In addition, BioMarin RareConnections™, a resource available to patients and families, provides a variety of personalized support services at no cost to patients, including education on CLN2 disease and Brineura, and coordination of additional services, such as information about financial assistance programs.

"We thank the FDA for recognizing Brineura's potential to alter the course of CLN2 disease and its urgency in delivering this treatment to children as quickly and safely as possible. Brineura was approved in under four years from starting the first clinical trial to today, a significant achievement for a condition that progresses so rapidly," said Jean-Jacques Bienaimé, Chairman and Chief Executive Officer of BioMarin. "Treating children with CLN2 disease requires an extraordinary amount of collaboration between families, hospitals, advocates and physicians. We are grateful for the partnership of all those involved and look forward to continuing to work together to make Brineura accessible to children who may benefit."

"CNL2 is a devastating diagnosis that robs families of life with their children much too young," said Emily de Los Reyes, M.D., attending pediatric neurologist at Nationwide Children's Hospital and principal investigator for Brineura studies. "Today's announcement gives my patients and their families hope."

"The approval of Brineura is an extraordinary medical breakthrough for the CLN2 Batten community who have been waiting for this moment for more than a century when the condition was first described," said Margie Frazier, PhD, LISW-S, Executive Director of Batten Disease Support and Research Association. "We appreciate BioMarin's commitment and partnership to the CLN2 Batten community and investing the resources needed to bring this pivotal treatment to families."

With this approval, the FDA also issued a Rare Pediatric Disease Priority Review Voucher, which confers priority review to a subsequent drug application that would not otherwise qualify for priority review. The rare pediatric disease review voucher program is designed to encourage development of new drugs and biologics for the prevention or treatment of rare pediatric diseases.

Brineura is expected to be available in the United States by early June, and BioMarin will begin promotion of Brineura immediately.

Last week, the Committee for Medicinal Products for Human Use (CHMP), the scientific committee of the European

Medicines Agency (EMA), adopted a positive opinion for the company's Marketing Authorization Application (MAA) for Brineura to treat children with Neuronal Ceroid Lipofuscinosis Type 2 (CLN2) disease, a form of Batten disease, which is also known as tripeptidyl peptidase 1 (TPP1) deficiency. The CHMP's recommendation is now referred to the European Commission (EC), which is expected to render its final decision by the second quarter of 2017.

Clinical Trial Results

The approval was supported by safety and efficacy data assessed over 96 weeks in a non-randomized, single-arm dose escalation clinical study of patients with CLN2 disease. Brineura treated patients were compared to untreated patients from a natural history cohort.

Patients were assessed for decline in the motor domain of the CLN2 Clinical Rating Scale. The scale measures performance of mobility with normal function being a score of 3 and no function being a score of 0. Decline was defined as having a sustained 2-point decline or an unreversed score of 0 in the motor domain of the CLN2 Clinical Rating Scale.

Twenty-four patients aged 3-8 years were enrolled in the clinical study. One patient withdrew after week 1 due to inability to continue with study procedures; 23 patients were treated with Brineura every other week for 48 weeks and continued treatment during the extension.

Results from the 96-week analysis demonstrated the odds of Brineura-treated patients not having a decline were 13 times the odds of natural history cohort patients not having a decline (Odds Ratio (95% Confidence Interval): 13.1 (1.2, 146.9)).

Of the 22 patients treated with Brineura and evaluated for efficacy at week 96, 21 (95%) did not decline, and only the patient who terminated early was deemed to have a decline in the motor domain of the CLN2 Clinical Rating Scale. In comparison, 50% of patients in an independent natural history cohort demonstrated progressive decline in motor function. Two Brineura treated patients with a maximum score were excluded from the analyses; they maintained that score throughout the study period.

In the clinical study, intraventricular access device-related infections were observed in two patients. In each case, antibiotics were administered, the intraventricular access device was replaced and the patient continued on Brineura treatment. Hypotension was reported in 2 (8%) patients, which occurred during or up to 8 hours after Brineura infusion. Patients did not require alteration in treatment and reactions resolved spontaneously or after IV fluid administration.

Hypersensitivity reactions have been reported in 11 (46%) Brineura treated patients during the clinical studies. The most common adverse reactions (≥8%) are pyrexia, ECG abnormalities, decreased cerebrospinal fluid (CSF) protein, vomiting, seizures, hypersensitivity, increased CSF protein, hematoma, headache, irritability, pleocytosis, device-related infection, bradycardia, feeling jittery, and hypotension.

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.

Conference Call and Web-cast to be Held Thursday, April 27 at 4:05 pm ET

Interested parties may access a live webcast that will accompany the conference call by going here. A replay of the call will be archived on the site for one week following the call.

U.S. / Canada Dial-in Number: (866) 502-9859
International Dial-in Number: (574) 990-1362
Conference ID: 14529654

Replay Dial-in Number: (855) 859-2056
Replay International Dial-in Number: (404) 537-3406
Conference ID: 14529654

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.

To reach a BioMarin RareConnections™ case manager, please call, toll-free, 1-866-906-6100 or e-mail support@biomarin-rareconnections.com. For more information about Brineura, please visit www.brineura.com. 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 patients with serious and life-threatening rare and ultra-rare genetic diseases. The Company's portfolio consists of six commercialized products and multiple clinical and pre-clinical product candidates. For additional information, please visit www.BioMarin.com.

Forward-Looking Statement

This press release contains forward-looking statements about the business prospects of BioMarin Pharmaceutical Inc., including, without limitation, statements about: expectations regarding the approval of Brineura, BioMarin's ability to support the launch of a new product and ship to specialty pharmacies, BioMarin's development programs for

Brineura generally, BioMarin's free genetic testing program and the services to be provided by BioMarin's RareConnections™ and the results of the Phase 1/2 pivotal trial and an ongoing extension studies of Brineura. 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: actions by regulatory agencies other than the FDA, results and timing of current and planned clinical trials of BioMarin's products, the risks related to the commercialization of Brineura, our ability to manufacture sufficient quantities of Brineura for clinical trials and the commercial launch of Brineura in the United States, the market potential for Brinuera as a treatment for CLN2 disease; and those other risks detailed from time to time under the caption "Risk Factors" and elsewhere in the Company's Securities and Exchange Commission (SEC) filings including the Annual Report on Form 10-K for the year ended December 31, 2016, and future filings and reports by the Company. The Company undertakes no duty or obligation to update any forward-looking statements contained in this Current Report on Form 8-K as a result of new information, future events or changes in its expectations.

Contacts:

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

SOURCE BioMarin Pharmaceutical Inc.
