BioMarin Announces Positive Data From Cerliponase Alfa Program for Treatment of CLN2 Disease, a Form of Batten Disease, at 12th Annual WORLDSymposium(TM) 2016

80% Reduction in Clinical Disease Progression in One Year Compared to Natural History (p <0.0001)
Company Plans to Submit Marketing Applications Starting Mid-Year 2016

SAN RAFAEL, Calif., March 02, 2016 (GLOBE NEWSWIRE) -- BioMarin Pharmaceutical Inc. (Nasdaq:BMRN) today announced positive 48-week results from its Phase 1/2 pivotal study for cerliponase alfa, a recombinant human tripeptidyl peptidase 1 (rhTPP1) to treat children with CLN2 disease, a form of Batten disease. CLN2 disease is a rapidly progressing, fatal neurodegenerative disease with no approved treatments, where the majority of affected children lose their ability to walk and talk by approximately six years of age. The average rate of clinical decline for motor and language function in patients receiving cerliponase alfa treatment — the primary efficacy endpoint — was approximately 80% less than the expected rate of decline in the untreated population, preserving essential function in the majority of treated patients (p <0.0001). Treatment with 300 mg cerliponase alfa administered via intracerebroventricular (ICV) infusion every other week was generally safe and well-tolerated in 24 patients and resulted in disease stabilization in 65% (15 of 23) of patients treated over a 48-week period, based on the Hamburg Motor + Language CLN2 rating. BioMarin estimates the incidence of CLN2 disease is approximately one in 200,000 with approximately 1,200 to 1,600 children in BioMarin's commercial territories.

In the phase 1/2 study, 87% of patients experienced attenuation of their disease compared to the expected rate of decline observed in available natural history data. The primary endpoint of the study is a standardized mobility (motor) and language score using a CLN2 disease-specific rating scale. The scale separately measures performance of mobility and language with normal function in each being a score of 3 and no function being a score of 0. The highest score possible is 6. Natural history of the disease shows an average of 2.1 units of decline over 48 weeks in 41 untreated patients followed longitudinally.[1] The mean decline in 21 evaluable subjects receiving cerliponase alfa treatment was 0.43 units over 48 weeks (p < 0.0001 compared to a 2-point/48 week decline derived from available natural history). Of the 23 evaluable subjects, two were not included in the rate of decline evaluation, as these subjects entered the study with the maximum motor-language score of 6, were not actively declining prior to treatment initiation and remained at 6 during the treatment period.

Brain Magnetic Resonance Imaging (MRI) measurement showed that cerliponase alfa treatment attenuated cortical grey matter volume loss. In 23 treated patients, the mean total cortical grey matter volume decrease is 9.7% over 48 weeks. In a separate study of six untreated children with CLN2 disease, cortical grey matter volume decreased by 14.5% each year.[2]

An interim analysis from an ongoing extension study suggests durability of therapeutic effect. The mean change from baseline in the first nine patients receiving cerliponase alfa treatment was an improvement of +0.2 units over 72 weeks compared to the expected decline observed in a natural history cohort of approximately -3.13 units. Of those nine patients, three gained 1 point, five remained with a stable score and one lost 1 point. In the four patients who received cerliponase alfa for up to 88 weeks, the mean change from baseline was a decline of -0.5 units compared to the expected decline observed in a natural history cohort of approximately -3.83 units.

Additional analysis of cerliponase alfa for the treatment of CLN2 disease will be presented at the International Child Neurology Congress in Amsterdam at the beginning of May.

"BioMarin is humbled by the substantial benefit that cerliponase alfa has shown for many of the children with CLN2 disease in this trial. Maintaining one or two points on the CLN2 disease-specific rating scale could mean the important difference between a child being able to continue to walk and talk or not," said Hank Fuchs, M.D., Chief Medical Officer of BioMarin. "We have pushed out a medical frontier by developing a potential first enzyme replacement therapy administered directly into the brain ventricles for a form of Batten disease. We are planning to apply for regulatory approval in the U.S. and Europe with this study, which is a very rapid registration approach justified by compelling data in this devastating disease."

"We have seen a highly significant impact for the children participating in this study. This demonstrates the important proof of principle that enzyme replacement therapy administered directly to the brain ventricles can be effective and presents a desperately awaited ray of hope for CLN2 patients worldwide," said Angela Schulz, M.D. Ph.D., Department of Paediatrics, University Medical Center Hamburg-Eppendorf. "It is a privilege to be part of the development of a therapy that has the potential to alter the course of CLN2 disease. I am thankful to the children and their families who uprooted their lives to participate in this groundbreaking study."

"We are hugely grateful to BioMarin for its continued commitment to developing a treatment for CLN2, late infantile

batten disease. For all those families who firmly held onto the hope of a treatment, this is very welcome and exciting news for a better future," said Andrea West, Chief Executive, Batten Disease Family Association.

"BioMarin continues a tradition of being a pioneer in enzyme replacement therapies with the development of a treatment for this form of Batten disease. The company is making an important effort to move through the regulatory process as quickly and efficiently as possible to make this needed therapy widely available," said Margie Frazier, Ph.D., Executive Director, Batten Disease Support and Research Association.

Safety Results from Study 190-201

Cerliponase alfa administered via intracerebroventricular infusion every 14 days was well tolerated, and no patients discontinued treatment due to adverse events (AEs). 23 of 24 patients who received more than one dose of drug completed the 48-week study and then chose to enroll in an extension study and continue to receive treatment. One subject discontinued treatment after one dose of drug due to inability to comply with all study procedures. Most AEs were Grade 1 or 2, and the majority are consistent with severe, chronic neurologic disease in pediatric patients. The most common events associated with treatment included: pyrexia (46%), hypersensitivity (33%), seizure (33%), epilepsy (17%), vomiting (13%) and headache (13%).

Seven (29%) of the subjects experienced a total of ten serious adverse events (SAEs) assessed as related to cerliponase alfa by the study investigators, which included eight events of hypersensitivity and two events of infusion-related reactions. Eight of the ten related SAEs were Grade 1 or 2 in severity, and two were Grade 3 (hypersensitivity). Seven (29%) patients experienced 15 device-related adverse events: 14 out of 15 were Grade 1 or 2. The only device-related SAE was a single report of a Grade 3 SAE (propionibacterium infection), which was detected by routine cerebrospinal fluid monitoring, was treated, and patient resumed drug treatment. There were no reports of anaphylaxis or anaphylactoid reactions, and no deaths during the study.

Efficacy Results from Study 190-201

Table 1: Baseline Characteristics

		Number of Subjects
Age (years) Mean (SD)	4.3 (1.24)	24
Baseline CLN2 Score (sum of motor and language)	6	2
	5	2
	4	6
	3	12
	2	2
Mean (SD), Median	3.6 (1.06), 3.0	

Table 2: Hamburg Motor + Language Rating Scale[1]

Motor:	Normal	3
	Clumsy, falls	2
	Non-walking	1
	Immobile	0
Language:	Normal	3
	Abnormal	2
	Minimal	1
	Unintelligible	0

[1] Simplified for presentation purposes

Table 3: Rate of Progression in Cerliponase Alfa Treated Patients Compared to Natural History Motor-Language Assessment

Rate of Decline (points/48 weeks)	Overall (n=21)*	2-sided p-value
n	21	<0.0001**
Mean (SD)	0.43 (0.84)	

Median	0.00

*21 evaluable subjects (Of the 23 evaluable subjects, two were not included in the rate of decline evaluation, as these subjects entered the study with the maximum motor-language score of 6, were not actively declining prior to treatment initiation and remained at 6 during the treatment period.)

**P-value computed as a two-sided t-test compared to a rate 2.0 units/48 weeks

Table 4. Change in Motor-Language CLN2 Scores from 300 mg Baseline to Last 300 mg Dose (> 48 weeks)

CLN2 Score Change from Baseline	Overall (n=23)	Percent Subjects	
3 (Improvement)	0		
2	0		
1	2	9	%
0 (No Change)	13	57	%
-1	5	22	%
-2	3	13	%
-3 (Worsening)	0		

Plans to Submit Marketing Applications

BioMarin plans to submit marketing applications with the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) by mid-year 2016 with anticipated actions by the FDA and EMA in the first half of 2017.

The FDA and EMA granted cerliponase alfa Orphan Drug Designation. In addition, the FDA granted cerliponase alfa with Breakthrough Therapy designation. BioMarin will seek to shorten the regulatory review time by requesting Priority Review in the U.S and Accelerated Assessment in Europe. Priority Review status is designated by the FDA to drugs that offer major advances in treatment or provide a treatment where no adequate therapy exists. Accelerated Assessment is designated by the EMA to drugs that are considered to be medicinal products of major therapeutic interest.

Phase 1/2 Study Design

The Phase 1/2 pivotal study is an open-label, dose-escalation study in patients with CLN2 disease between three and 16 years of age. The primary objectives are to evaluate the safety and tolerability of ICV-administered cerliponase alfa and to evaluate effectiveness using a CLN2 disease-specific rating scale score in comparison with natural history data after 48 weeks of treatment. Secondary objectives are to evaluate the impact of treatment on brain atrophy using a secondary efficacy end point of cranial volume measurements by MRI and to characterize pharmacokinetics and immunogenicity. The study enrolled 24 subjects at five clinical sites. Subjects were administered a stable dose of cerliponase alfa (300 mg by ICV infusion every 14 days) for at least 48 weeks.

Early Access Program

BioMarin is planning to implement an early access program to provide access to treatment for additional CLN2 patients prior to obtaining marketing approval. An early access program will be limited in scope and number of participants, and will be conducted under a protocol. We expect that the program will be conducted at centers that have participated in the cerliponase alfa study. Those sites have experience administering this drug directly to the brain and would ensure continued patient monitoring. The program is expected to begin in Q3 2016. The exact timing will vary by country of the sites participating. The overall scope, eligibility criteria and details of this program are still being determined. BioMarin must adhere to specific legal procedures for each country and has begun these preparations at risk with the goal of being ready to dose patients in Q3 2016. BioMarin will provide additional details about the scope and timing of this program as they become available.

About Cerliponase Alfa

Cerliponase alfa is a recombinant form of human 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 to the fluid surrounding the brain (cerebrospinal fluid) using BioMarin's patented technology.

For additional information regarding the investigational product cerliponase alfa, please contact BioMarin Medical Information at medinfo@bmrn.com.

About CLN2 Disease

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/CLN2 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. Disease progression is rapid. The onset of symptoms is typically between ages two and four. Patients typically present initially with language delay and seizures, followed by movement disorders, motor deterioration, dementia, blindness and early death. During the later stages of the disease, feeding and tending to everyday needs become very difficult and death typically occurs between ten and 16 years of age.

There is no approved treatment that can prevent, stop, or reverse CLN2 disease. Symptomatic care to treat the symptoms of the disease, prevent and treat complications, and attempt to preserve quality of life is the only available treatment options for patients with this rare disease.

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 five commercialized products and multiple clinical and pre-clinical product candidates.

For additional information, please visit www.BMRN.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., including, without limitation, statements about: BioMarin's development programs for cerliponase alfa generally, and specifically about the results of the Phase 1/2 pivotal trial and an ongoing extension study of cerliponase alfa. 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 of current and planned clinical trials of cerliponase alfa; the content and timing of decisions by the U.S. Food and Drug Administration, the European Medicines Agency and other regulatory authorities; our ability to manufacture sufficient quantities of cerliponase alfa for clinical trials, commercial launch and other preapproval requirements; 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" in BioMarin's 2015 Annual Report on Form 10-K, as amended, and the factors contained in BioMarin's reports on Form 8-K. 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.

BioMarin® is a registered trademark of BioMarin Pharmaceutical Inc.

[1] Nickel M, Jacoby D, Lezius S, Down M, Genter F, Wittes J, Kohlschütter A, Schulz, A Natural history of CLN2 disease: Quantitative assessment of disease characteristics and rate of progression, poster presented at WORLD*Symposium* 2016

[2] Löbel et al, Brain volumetry and clinical scoring in patients with CLN2 disease: an objective tool to monitor disease progression, poster presented at WORLD*Symposium* 2016

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