BioMarin Announces Kuvan Significantly Improves Inattentiveness in Kuvan Responding PKU Patients

SAN RAFAEL, Calif., Feb. 19, 2013 (GLOBE NEWSWIRE) -- BioMarin Pharmaceutical Inc. (Nasdaq:BMRN) announced today results from the PKU-016 ASCEND study, the largest randomized controlled trial evaluating neuropsychiatric outcomes in phenylketonuria (PKU) patients treated with the approved drug Kuvan (sapropterin dihydrochloride).

The study evaluated medically important symptoms similar to attention deficit hyperactivity disorder (ADHD) in PKU patients whose blood levels of phenylalanine (Phe) are reduced by Kuvan. The primary endpoint of the study was evaluated using an attention deficit hyperactivity rating scale (ADHD-RS), commonly used to evaluate symptoms of inattentiveness and hyperactivity. Kuvan improved the ADHD-RS ($p=0.085$), driven by a statistically significant change in the inattention component of the score ($p=0.036$). PKU patients have a lower degree of hyperactivity as compared to ADHD patients, which likely resulted in the less prominent benefits in this domain. The neurocognitive benefit of Kuvan in patients who respond to Kuvan was corroborated by the Behavior Rating Inventory of Executive Function, or BRIEF, in children who were rated by their parents. Moderate to severe inattention deficit affected approximately one-third of patients in the study. Preliminary analysis of safety indicates that it is consistent with the general experience with Kuvan.

"We are encouraged to see the positive trend in the predetermined ADHD primary endpoint, which was driven by a statistically significant change in the sub-domain of inattentiveness," said Hank Fuchs, M.D., Chief Medical Officer of BioMarin. "We believe these results will provide useful information to the medical community on clinically relevant benefits of Kuvan and facilitate adoption of the product. Further, the results will help inform the design of the Phase 3 PEG-PAL program with key learnings about the measurement tools. We are encouraged by the results and plan to discuss the submission of this data with the FDA for possible inclusion in the Kuvan label."

In addition to the ADHD-RS and BRIEF instruments, other exploratory tests in the PKU-016 study of neuropsychiatric deficit in PKU patients demonstrated a higher level of impairment in PKU patients than the normal population. Further analyses are underway to complete the evaluation of Kuvan on these outcome measures.

Dr. Robert Hendren, Professor and Vice Chair of Psychiatry and Director of Child and Adolescent Psychiatry at the University of California, San Francisco commented, "These data document what has been known by PKU clinicians for a long time; namely, mental health impairment is a prevalent and important problem affecting PKU patients and that improved control of their metabolic condition translates into improved control of the impairment in mental health."

Abstracts will be submitted to the International Congress of Inborn Errors of Metabolism (ICIEM) and American Society of Human Genetics (ASHG) meetings this fall.

Study Design

PKU-016 is a double-blind, placebo-controlled, randomized study to evaluate the safety and therapeutic effects of Kuvan on neuropsychiatric symptoms in subjects with PKU. The study enrolled 206 patients, 118 of whom are responders to Kuvan as determined by a drop in blood Phe levels. The study includes a two-week screening period, a 13-week double-blind randomized treatment period and a 13-week open-label treatment period at a dose of 20 mg/kg/day.

The Attention Deficit Hyperactivity Disorder Rating Scale (ADHD-RS) is an instrument for assessing treatment response in patients who do not have metabolic disorders causing inattention and hyperactivity. The scale has been widely used to evaluate therapies approved for ADHD in patients without metabolic brain disease. Because inattention observed in PKU patients is similar in clinical presentation, the ADHD-RS was used to measure outcomes.

The Behavior Rating Inventory of Executive Function (BRIEF) rating scale is an instrument to assess executive function behaviors. The 86-item questionnaire forms a Global Executive Composite, which is comprised of two indices: Behavioral Regulation and Metacognition and eight sub-domains exploring specific deficits in executive functioning.

Placebo Kuvan

All patients (N)	108	98	Total= 206
Kuvan responders (N)	57	61	Total =118
ADHD-like Kuvan responders (N)	19	19	Total = 38
Change from baseline ADHD-RS	-5.4	-9.5	Difference = -4.1 (in favor of Kuvan) p=0.085, Kuvan versus placebo
Change from baseline inattentiveness domain	-2.6	-6.0	Difference -3.4 (in favor of Kuvan) p=0.036, Kuvan versus placebo

About BioMarin

BioMarin develops and commercializes innovative biopharmaceuticals for serious diseases and medical conditions. The company's product portfolio comprises four approved products and multiple clinical and pre-clinical product candidates. Approved products include Naglazyme® (galsulfase) for mucopolysaccharidosis VI (MPS VI), a product wholly developed and commercialized by BioMarin; Aldurazyme® (laronidase) for mucopolysaccharidosis I (MPS I), a product which BioMarin developed through a 50/50 joint venture with Genzyme Corporation; Kuvan® (sapropterin dihydrochloride) Tablets, for phenylketonuria (PKU), developed in partnership with Merck Serono, a division of Merck KGaA of Darmstadt, Germany; and Firdapse™ (amifampridine), which has been approved by the European Commission for the treatment of Lambert Eaton Myasthenic Syndrome (LEMS). Product candidates include BMN-110 (N-acetylgalactosamine 6-sulfatase), formally referred to as GALNS, which successfully completed Phase III clinical development for the treatment of MPS IVA, PEG-PAL (PEGylated recombinant phenylalanine ammonia lyase), which is currently in Phase II clinical development for the treatment of PKU, BMN-701, a novel fusion protein of insulin-like growth factor 2 and acid alpha glucosidase (IGF2-GAA), which is currently in Phase I/II clinical development for the treatment of Pompe disease, BMN-673, a poly ADP-ribose polymerase (PARP) inhibitor, which is currently in Phase I/II clinical development for the treatment of genetically-defined cancers, and BMN-111, a modified C-natriuretic peptide, which is currently in Phase I clinical development for the treatment of achondroplasia. For additional information, please visit www.BMRN.com. Information on BioMarin's website is not incorporated by reference into this press release.

The BioMarin Pharmaceutical Inc. logo is available at http://www.globenewswire.com/newsroom/prs/?pkgid=11419

Forward-Looking Statement

This press release contains forward-looking statements about the business prospects of BioMarin Pharmaceutical Inc., including, without limitation, statements about: regulatory actions related to Kuvan, the development of BioMarin's PEG-PAL program generally, the design of the planed Phase 3 trial of PEG-PAL, and expectations regarding the final results of the ASCEND trial following final statistical analysis, the impact of the ASCEND trial on Kuvan adoption. 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: differences in the final analysis of the data from the ASCEND trial, results and timing of current and planned preclinical studies and clinical trials of PEG-PAL; the content and timing of decisions by the U.S. Food and Drug Administration, particularly as related to any amendment to the Kuvan label, the European Commission and other regulatory authorities; physicians' interpretation of the relevance of the final trial data and its impact on their prescribing practices; 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 Quarterly Report on Form 10-Q for the Quarter ended September 30, 2012. 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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