

# BioMarin Phase 3 Study of Pegvaliase for Phenylketonuria (PKU) Meets Primary Endpoint of Blood Phenylalanine (Phe) Reduction ( $p < 0.0001$ )

**In 8-week Placebo-Controlled Portion No Benefit in Inattention or Mood Scores Were Observed Approximately, 60% of Patients Maintained Phe Levels At or Below Medical Guidelines over Long-Term Extension Study**

**Conference Call and Webcast with Slides to Be Held Today at 8:30 AM ET**

SAN RAFAEL, Calif., March 21, 2016 (GLOBE NEWSWIRE) -- BioMarin announced today that the pivotal Phase 3 PRISM-2 study (formerly referred to as 165-302) of pegvaliase met the primary endpoint of change in blood Phe compared with placebo ( $p < 0.0001$ ) in preliminary results. During the 8 week PRISM-2 double-blind, placebo-controlled, randomized drug discontinuation trial (RDT), 86 patients were randomized to either remain on pegvaliase or receive matching placebo. The pegvaliase treated group maintained mean blood Phe levels at 527.2 umol/L compared to their RDT baseline of 503.9 umol/L, whereas the placebo treated group mean blood Phe levels increased to 1385.7 umol/L compared to their RDT baseline of 536.0 umol/L. (see Table 1) The treatment effect demonstrated in this study represents an approximately 62% improvement in blood Phe compared to placebo.

This is the first placebo controlled study demonstrating the ability to improve Phe levels in PKU patients who at baseline do not have to follow a Phe-restricted diet. Typically, a Phe-restricted diet does not allow any protein intake outside of medical food. Patients in the trial were estimated to be eating 75% of the daily recommended allowance for protein intake for a healthy adult.

In the secondary endpoints of the 8 week RDT, no benefit in inattention or mood scores were observed in patients treated with pegvaliase compared to placebo. In an exploratory sub study of cognitive function in 9 patients, the Cambridge Neuropsychological Test Automated Battery (CANTAB) showed trends of improvement favoring pegvaliase. (see Table 2)

In contrast to the short term results of the RDT, supportive evidence of the association of reduced blood Phe and improvement in inattentiveness comes from two long term evaluations in the PRISM-1 and PRISM-2 studies. In these studies, ADHD-RS assessments were obtained prior to treatment and at various times thereafter (scale range 0-27 points, higher score indicating greater impairment). In the open label PRISM-1 study (formerly referred to as 165-301 or feeder study), 49 patients had baseline inattention scores greater than 9 (defining patients with inattentive symptoms at baseline). Of the 35 patients whose Phe was reduced during PRISM-1 by greater than 20%, the mean improvement in inattention was 7.3 points, while the 14 patients whose Phe was reduced by less than 20% only showed an improvement of 3.7. (see Table 3).

In the PRISM-2 study, the 72 patients were evaluated regardless of the baseline scores. Among those who completed 41 weeks in the open-label extension, patients were divided into quartiles based on the magnitude of their Phe reduction from baseline. The quartile of patients having the largest Phe reductions (to values lower than  $\geq 1,296$  umol/L) had mean improvements in their ADHD-RS inattention score of 7.5 while the patients with the smallest Phe reductions (to values no less than  $< 289$  umol/L) had mean improvements in the inattention score of 3.2. (See Table 4).

Practice guidelines issued by the American College of Medical Genetics and Genomics (ACMG) support the need for lifelong management of Phe levels in patients with phenylketonuria or PKU. The guidelines state that the treatment goal for PKU patients should be blood levels of phenylalanine (Phe) for all patients between 120-360 umol/L. The Long Term open label portion of the PRISM-2 study demonstrated sustained and substantial reductions in Phe levels. Of the 90 patients who had been treated for at least 41 weeks in this portion of PRISM-2, 40% had achieved a Phe level of 120 umol/L or less (120 umol/L is considered the upper limit of normal), 60% had achieved a Phe level of 360 umol/L or lower (the target Phe level according to the ACMG guidelines) and 79% had achieved a Phe level reduction of 20% or greater.

PRISM-1 and PRISM-2 studies are the phase 3 studies evaluating blood Phe in PKU patients treated with pegvaliase. PRISM-1 was an open-label study which enrolled and randomized pegvaliase naïve adult PKU patients to a target dose of pegvaliase 20mg/day or 40mg/day. Patients were treated in an induction, titration, maintenance dosing regimen to achieve stable, reduced blood Phe levels. Patients who met a pre-specified reduction in blood Phe of at least 20% (based on two consecutive assessments) from their pre-treatment baseline in the PRISM-1 feeder study were eligible to enter the RDT of the PRISM-2 study, where patients were randomized to continue on their target dose of pegvaliase or to receive matching placebo.

In the PRISM-2 RDT, no subjects discontinued study drug due to adverse events and pegvaliase was generally well tolerated compared to placebo. Pegvaliase treated patients had more hypersensitivity adverse events (39%) as compared to placebo (14%). During the 8 week RDT phase there were no anaphylaxis events as defined by the broad National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network (NIAID/FAAN) (Sampson's) criteria. The most frequent adverse events were arthralgia (pegvaliase 14% vs placebo 10%), headache

(pegvaliase 12% vs placebo 24%), fatigue (pegvaliase 11% vs placebo 10%). In the PRISM-2 long term open label extension, the most common adverse events were arthralgia (28%), headache (24%), and injection site reaction (23%).

In PRISM-1, hypersensitivity adverse events and anaphylaxis as defined by the broad NIAID/FAAN criteria were higher during the initial treatment phase and then decreased over time as patients reached stable dosing. Across the entire Phase 3 program, including the PRISM-1 and the PRISM-2 studies, 8% of patients had anaphylaxis by the broad NIAID/FAAN criteria. 48% of patients with anaphylaxis were safely rechallenged and continued dosing with pegvaliase without further anaphylaxis episodes.

The safety data set for all pegvaliase trials includes approximately 550 patient years of treatment, 300 of which are from the Phase 3 program. Approximately 190 patients have been treated with pegvaliase for more than a year, 105 patients have been treated for more than two years and 46 have been treated more than three years.

These studies will be presented at the Society of Inherited Metabolic Disorders in April of 2016.

BioMarin intends to submit a marketing application by the end of the year subject to further discussions with the FDA.

"We are pleased that the double-blind, randomized, placebo-controlled part of the PRISM-2 trial demonstrated strong blood Phe reduction in pegvaliase treated patients whose dietary protein intake was unrestricted at baseline and maintained throughout the study. We are committed to the global PKU community and to bringing them a medicine that has the potential to treat PKU adult patients," said Hank Fuchs, M.D., Chief Medical Officer at BioMarin. "We look forward to sharing this data with the regulatory authorities in the US and Europe to continue the process of bringing an important therapy to patients."

"Treatment with pegvaliase has resulted in dramatic Phe decreases down to within normal levels which have not been achievable in the past with other PKU treatment options. We are grateful to the patients who participated in this important trial. Blood Phe reductions at this level have the potential to have a meaningful impact on the lives of PKU patients," said Cary Harding, M.D. Professor of Molecular and Medical Genetics and Pediatrics at Oregon Health & Science University and investigator for the pegvaliase Phase 3 program.

"A therapy in development that shows such a substantial reduction in Phe levels could mean that for the first time, PKU patients who cannot comply with dietary protein restriction, can achieve targeted blood Phe levels," said Barbara Burton, M.D., Professor of Pediatrics-Genetics, Birth Defects and Metabolism at Northwestern School of Medicine and investigator for the pegvaliase Phase 3 program. "This pegvaliase study represents an important advance for PKU adult patients and a potentially meaningful treatment."

**Table 1: Observed Blood Phe Concentration at Treatment Naïve Baseline, Start and End of RDT (mITT Population)**

	Treatment Naïve Baseline	RDT Baseline	RDT Week 8	
			Active	Placebo
N	86	86		
Mean (µmol/L)	1306.9	514.3**	527.2	1385.7
p-value*			< 0.0001	

mITT: modified intent-to-treat; Phe: phenylalanine; RDT: randomized discontinuation trial.

\* P-value from the mixed-effect model repeated measure (MMRM) model for comparison of change in blood Phe concentration from RDT baseline to Week 8 between the pooled active arm and the pooled placebo arm. RDT Week 4 assessments were included in the modeling.

**Table 2: Summary of Secondary Efficacy Endpoints in RDT and Efficacy Endpoints in Exploratory Sub Study of Cognitive Function**

Study	Efficacy Endpoints*	Results (Active — Placebo)		
		N (Active/Placebo)	Difference in LS Mean (95% CI)	p-value
<b>RDT** (Part 2 of 165-302)</b>	ADHD-RS Inattention Subscale Scores (Treatment Naïve Baseline > 9)	26 / 11	2.74 (-0.27, 5.75)	0.0734

	ADHD-RS Inattention Subscale Scores	58 / 28	0.71 (-1.21, 2.62)	0.4634
	PKU POMS Confusion Subscale Scores	58 / 28	-0.37 (-1.46, 0.73)	0.5074
	PKU POMS TMD Scores	58 / 28	-0.28 (-6.05, 5.49)	0.9226
	POMS Self-rated TMD Scores	58 / 28	2.87 (-10.10, 15.84)	0.6606
<b>Sub Study*** (165-303)</b>	Rapid Visual Processing (RVP) Mean Response Latency	6 / 3	-72 (-145, 1)	0.0719
	Stop Signal Task (SST) Stop Signal Reaction Time (ms)	6 / 3	-64 (-122, -6)	0.0497
	Spatial Working Memory (SWM) Between Errors 4-8 Boxes	6 / 3	-9 (-21, 3)	0.1377

ADHD-RS: attention deficit hyperactivity disorder rating scale; CI: confidence interval; LS: least square; PKU: phenylketonuria; POMS: profile of mood states; RDT: randomized discontinuation trial; TMD: total mood disturbance.

\* Lower is better for all efficacy endpoints.

\*\* P-value from the mixed-effect model repeated measure (MMRM) model for comparison of change from RDT baseline to Week 8 between the pooled active arm and the pooled placebo arm. RDT Week 4 assessments were included in the modeling.

\*\*\* Pooled active had a mean increase in blood Phe of 75 umol/L vs. pooled placebo had a mean increase of 1,201 umol/L.

**Table 3: Change in ADHD-RS Inattention in PRISM 1 and PRISM 2 Part 1 in Subjects with Naïve Baseline Inattention >9**

	Sample Size	PRISM 1 Baseline Mean (SD)	PRISM 1 End of Study/PRISM 2 Part 1 Mean (SD)	Change from baseline to end of study Mean (SD)
Patients with >20% reduction in blood Phe in PRISM-1	35	15.5 (4.18)	8.1 (4.45)	-7.3 (6.16)
Patients without 20% Phe reduction in PRISM-1	14	14.0 (4.30)	10.3 (6.27)	-3.7 (5.01)

**Table 4: Correlation of Change from Naïve Baseline to Open Label Extension at Week 41 between Blood Phe Concentration and ADHD Inattention Subscale Score in PRISM 2**

Reduction in Value* from Treatment Naïve Baseline to Open Label Extension at Week 41	Blood Phe Concentration (µmol/L) by Quartile (range)			
	Quartile 1 >1,296 More reduction	Quartile 2 (837 to 1,295)	Quartile 3 (290 to 836)	Quartile 4 < 289 Less Reduction

**ADHD Inattention  
Subscale Score****N = 72**

Mean	7.5	6.5	5.4	3.2
Min, Max	-1, 19	-2, 17	-6, 21	- 7, 10

ADHD-RS: attention deficit hyperactivity disorder rating scale.

\* Numbers with a minus sign indicate increase in value from treatment naïve baseline to Part 4 Week 41.

**Phase 3 Study Design**

The Phase 3 program consists of two studies. PRISM-1 study was a Phase 3 open-label, randomized, multi-center study that enrolled 261 patients, and its primary objective was to characterize the safety and tolerability of pegvaliase during induction, titration, and maintenance dosing. The secondary objective of the study was to evaluate blood Phe levels during induction, titration, and maintenance dosing to achieve a target dose of pegvaliase 20mg/day or 40mg/day.

215 patients who completed PRISM-1 or PAL-003 (Phase 2 long term extension) enrolled into PRISM-2, which included a randomized, double-blind, placebo-controlled discontinuation study to evaluate the efficacy and safety of subcutaneous injections of pegvaliase self-administered by adults with PKU, followed by an open-label extension. The primary efficacy endpoint is change from the RDT baseline in blood Phe at eight weeks.

Patients who reached a target dose and achieved  $\geq 20\%$  decrease in blood Phe from PRISM-1 baseline were randomized into the RDT portion of the study to either continue their pegvaliase dose or to start matching placebo. Those participants not reaching a  $\geq 20\%$  reduction in blood Phe from PRISM-1 baseline skipped the RDT and enrolled into the open label extension portion of the study. In the open-label extension, physicians were allowed to modify dose based on blood Phe response using a range of doses from 10 mg/day to 60 mg/day. Patients were evaluated for changes in Phe levels and inattention and mood symptoms.

**About Pegvaliase**

Pegvaliase is an investigational study drug that substitutes the PAH enzyme in PKU by breaking down Phe. It is being developed as a potential treatment for adults with inadequately controlled blood Phe levels

For additional information regarding the investigational product pegvaliase, please contact BioMarin Medical Information at [medinfo@bmrn.com](mailto:medinfo@bmrn.com).

**About Phenylketonuria or Phenylalanine Hydroxylase Deficiency**

Phenylketonuria (PKU) or phenylalanine hydroxylase (PAH) deficiency is a genetic disorder affecting approximately 50,000 diagnosed patients in the developed world and is caused by a deficiency of the enzyme PAH. This enzyme is required for the metabolism of Phe, an essential amino acid found in most protein-containing foods. If the active enzyme is not present in sufficient quantities, Phe accumulates to abnormally high levels in the blood and becomes toxic to the brain, resulting in a variety of complications including severe intellectual disability, seizures, tremors, behavioral problems and psychiatric symptoms. As a result of newborn screening efforts implemented in the 1960s and early 1970s, virtually all individuals with PKU or PAH deficiency under the age of 40 in developed countries are diagnosed at birth and treatment is implemented soon after. PAH deficiency can be managed with a Phe-restricted diet, which is supplemented by low-protein modified foods and Phe-free medical foods; however, the strict diet is difficult for most patients to adhere to the extent needed for achieving adequate control of blood Phe levels. To learn more about PKU and PAH deficiency, please visit [www.PKU.com](http://www.PKU.com). Information on this website is not incorporated by reference into this press release.

Some of the signs and symptoms of high blood Phe include:

- For infants and children: severe intellectual disability and developmental delay, skin rash (eczema), light-colored skin, eyes and hair (hypopigmentation)
- For teens and adults: lower intelligence, psychological and psychiatric symptoms like anxiety, depression and phobias, problems with memory and performing tasks (executive function), poor concentration and irritable mood among other things.
- For pregnant women: increased risk for the baby's growing brain, including risk of intellectual disability, increased risk for a small head (microcephaly) and other problems such as a heart malformation (congenital heart defect) and poor overall growth (intrauterine growth retardation). This teratogenic effect of Phe on the developing fetus is called Maternal PKU syndrome.

**About ACMG Guidelines**

Practice guidelines issued by the American College of Medical Genetics and Genomics (ACMG) support the need for lifelong management of Phe levels in patients with phenylketonuria or PKU. The new diagnosis and management guidelines were published online in Genetics In Medicine's Advance Online Publication (AOP) service and provide the

first update to recommendations for therapy of PKU since the 2001 National Institutes of Health Consensus statement.

The guidelines state that treatment of PKU should be initiated as early as possible and must be continued throughout adulthood and "lifelong," with a goal of maintaining blood levels of Phe for all patients between 120-360 umol/L. Patients treated from the early weeks of life with initial good metabolic control, but who lose that control in later childhood or adult life, may experience both reversible and irreversible neuropsychiatric consequences.

According to the guidelines "the primary goal of therapy is to lower blood Phe, and any interventions, including medications, or combination of therapies that help to achieve that goal in an individual, without other negative consequences, should be considered appropriate therapy."

Evidence for the guidelines are drawn from two previous independent review processes from the National Institutes of Health (2001) and the Agency for Health Research and Quality (2012). The guidelines can be accessed online at:

[https://www.acmg.net/docs/Phenylalanine\\_Hydrosylase\\_Deficiency\\_Practice\\_Guideline\\_AOP\\_Jan\\_2013.pdf](https://www.acmg.net/docs/Phenylalanine_Hydrosylase_Deficiency_Practice_Guideline_AOP_Jan_2013.pdf)

## **Conference Call Details**

BioMarin will host a conference call and live audio webcast today at 5:30am PDT/8:30am EDT to discuss Phase 3 results with pegvaliase. The live audio webcast will be available via the Investors and Media section of the BioMarin Pharmaceutical website at [www.BMRN.com](http://www.BMRN.com). Interested parties may now access the PowerPoint presentation that will be used for the call at the same URL. A replay will be available for one week following the call.

U.S. / Canada Dial-in Number: (877) 303-6313  
International Dial-in Number: (631) 813-4734  
Conference ID: 71342573

Replay Dial-in Number: (855) 859-2056  
Replay International Dial-in Number: (404) 537-3406  
Conference ID: 71342573

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

For additional information, please visit [www.BMRN.com](http://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 pegvaliase generally, and specifically about the results of the Phase 3 pivotal trial and an ongoing extension study of pegvaliase. 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: final analysis of PRISM 1 and PRISM 2 trial data; results and timing of current and planned clinical trials of pegvaliase; 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 pegvaliase 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.

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