BioMarin Accelerates Development of Phenoptin, a Novel Oral Enzyme Cofactor for the Treatment of PKU

If Approved, Phenoptin Could Become the First Prescription Drug for the Treatment of PKU
Manufacturing and Development Partnership Established with Merck Eprova AG, a Subsidiary of Merck KGaA

PRNewswire-FirstCall
NOVATO, Calif.

BioMarin Pharmaceutical Inc. announced plans to begin clinical trials with Phenoptin(TM), an enzyme cofactor that is a second generation, proprietary oral form of tetrahydrobiopterin, for the treatment of phenylketonuria (PKU). PKU is a genetic disease that affects at least 50,000 patients under the age of 40 in the developed world. If approved, Phenoptin could become the first prescription drug for the treatment of PKU. The company also announced that it has entered into a partnership agreement with Merck Eprova AG (www.eprova.com), a subsidiary of Merck KGaA, for the manufacturing and supply of Phenoptin.

"Phenoptin represents an outstanding strategic fit with the other products in our pipeline; it is enzyme-related, builds upon our experience in developing products for pediatric diseases, and is in line with our commercial focus on pediatricians and medical geneticists," stated Fredric D. Price, Chairman and Chief Executive Officer of BioMarin. "Phenoptin, taken orally, could be useful for PKU patients with mild to moderate forms of the condition, which represents approximately half of the PKU population. We expect to begin clinical trials with Phenoptin in 2004, and we continue to make progress with Phenylase(TM), an injectable enzyme in preclinical development, that could address patients with PKU who cannot respond to Phenoptin."

Mr. Price continued, "As a second generation product, Phenoptin could be a significant improvement over tetrahydrobiopterin, which has demonstrated success in reducing high levels of phenylalanine (Phe), in published clinical studies. High Phe levels lead to the neurological problems seen in PKU. Phenoptin offers significant advantages over first generation tetrahydrobiopterin including improved stability and a commercially scaleable, more efficient manufacturing process that will enable BioMarin to make it widely available at a lower cost. If approved, Phenoptin could become the first prescription drug on the market for the treatment of PKU.

"Importantly, all of the development costs associated with both Phenoptin and Phenylase have already been incorporated in our previous guidance of both net loss and cash burn for the rest of 2003 and for all of 2004.

"We are building what we believe is a strong proprietary position for Phenoptin, beginning with Merck Eprova's patented microcrystalline stabilization technology and extending to manufacturing and use patent applications. We have also filed for orphan status in the United States (US) and the European Union (EU). In addition, we have a strong proprietary position on Phenylase, including 12 issued patents and seven patent applications related to the gene sequence, and methods of use and production of Phenylase. Under orphan drug law, should Phenoptin or Phenylase be approved, each would receive exclusivity for seven and 10 years in the US and EU, respectively.

"As Phenoptin represents our first small molecule development program, we are delighted to be working with Merck Eprova, whose small molecule manufacturing expertise is widely recognized. The partnership with Merck Eprova is structured to provide incentives to produce Phenoptin at the lowest possible cost. We look forward to working with Merck Eprova in an effort to bring this important product to PKU patients."

Charles R. Scriver, MDCM, Alva Professor Emeritus of Human Genetics at McGill University, Montreal Children's Hospital Research Institute, stated, "This is an important first step to address a long-standing need for a subset of patients with PKU or hyperphenylalaninemia. Phenoptin could become the next most important advance in the treatment of PKU since dietary restriction was discovered, leading to a higher quality of life, improved nutrition, and better neurological outcomes. The clinical results of tetrahydrobiopterin therapy to date have been promising, but the compound has been expensive, difficult to obtain, and is not approved for use as a therapeutic. The PKU community welcomes BioMarin's effort to make, develop and commercialize this second generation product, an improved form of tetrahydrobiopterin for PKU patients."

About Phenoptin

Phenoptin (6R-BH4) is a novel formulation of the naturally occurring enzyme cofactor tetrahydrobiopterin (BH4) in the stereochemically pure 6R form. Tetrahydrobiopterin is an essential enzyme cofactor required for

metabolism of several amino acids, including Phe. Published and reported studies indicate that tetrahydrobiopterin increases metabolism of Phe in a large fraction of PKU patients. Tetrahydrobiopterin has also been used to successfully treat BH4 deficiency, a metabolic condition related to PKU, for over 20 years. Historically, tetrahydrobiopterin has been difficult and expensive to manufacture, costing approximately $30,000 per year for an adult patient.

The BioMarin and Merck Eprova Partnership

To support development of Phenoptin, BioMarin has entered into a development and manufacturing agreement with Merck Eprova AG, a wholly-owned subsidiary of Merck KGaA of Darmstadt, Germany. Merck Eprova specializes in the synthesis development and commercial manufacturing of pterins, a class of molecules that includes Phenoptin. Merck Eprova and BioMarin have designed a proprietary, scalable, and cost-effective manufacturing process for 6R-BH4 that could result in an improved and less costly product for use in PKU. Merck Eprova will supply Phenoptin to BioMarin for clinical trials and potential commercial operations. The companies have filed patent applications on the manufacturing process, formulation, and uses of Phenoptin.

Under the terms of the agreement, BioMarin and Merck Eprova will share process development and clinical manufacturing costs, and BioMarin will own and develop the 6R-BH4 product for PKU and other genetic disease indications. BioMarin has a worldwide exclusive license on intellectual property relating to the synthesis, stabilization and use of 6R-BH4 for PKU and other genetic disease indications, and has right of first refusal to develop 6R-BH4 for cardiovascular and other indications. BioMarin will pay Merck Eprova a royalty (dependent on specified manufacturing cost targets) on commercial sales of Phenoptin for PKU or related indications.

BioMarin's Development Rationale for Phenoptin

-- PKU represents an important unmet medical need that affects at least 50,000 diagnosed people under the age of 40 in developed countries.

From 1997 to 2002, an average of approximately 1 in 14,000 new births per year were diagnosed with PKU in the US and about 1 in 10,000 in Europe. PKU incidence varies considerably by country in Europe and data from published studies indicate an incidence range of approximately 1 in 4,500 to 1 in 20,000. The vast majority of newborns in the developed world have been screened for PKU since the 1960s and early 1970s. Therefore, virtually all PKU patients under the age of 40 in developed countries have been diagnosed at birth.

-- Phenoptin could become the first approved pharmaceutical for the treatment of PKU.

To control Phe blood levels, people with PKU must adhere to a highly restrictive and unpalatable low-Phe diet. Compliance with a low-Phe diet is difficult, especially during and beyond adolescence, and as well as for those who have been off a restricted diet for extended periods. Formulated Phe diets are also costly, generally reimbursed by healthcare providers in the range of $7,000 to $10,000 per year. In October 2000, a Consensus Panel convened by the National Institutes of Health (NIH), concluded that all people with PKU should adhere to a restricted diet for their entire lives. Previously, the recommendation for a low-Phe diet was largely focused on children due to the high risk of severe mental retardation that can result from untreated PKU. The NIH consensus statement was based on an increasing number of reports that indicate that adult PKU patients who abandon the dietary Phe restriction can experience significant neurological and psychological problems.

-- The underlying pathophysiology of PKU and biochemistry of tetrahydrobiopterin are well understood, suggesting a clear-cut clinical development profile for Phenoptin. Since 1999, investigators evaluating tetrahydrobiopterin for PKU have demonstrated positive clinical results.

Tetrahydrobiopterin is a naturally occurring enzyme cofactor required for normal metabolism of several amino acids, including Phe. Tetrahydrobiopterin has been used to successfully treat BH4 deficiency, a rare metabolic disease also caused by high Phe levels, for approximately 20 years. Several recent studies indicate that approximately 30 to 50 percent of PKU patients are tetrahydrobiopterin-responsive. In 1999, researchers discovered that a highly purified 6R form of tetrahydrobiopterin, which

contained lower levels of the 6S isomer than in prior formulations, enhanced tetrahydrobiopterin responsiveness in people with PKU. Prior to this time, tetrahydrobiopterin contained a larger fraction of the 6S isomer that has been demonstrated to inhibit Phe metabolism. Phenoptin will be a highly purified formulation of the 6R isomer of tetrahydrobiopterin.

Published studies indicate that tetrahydrobiopterin is generally well tolerated in PKU and BH4-deficient patients. It has been used broadly in infants, children and adults with PKU in single and multiple doses. More than 350 patients with BH4 deficiency have been treated with tetrahydrobiopterin over the last 20 years.

-- A therapeutic for PKU fits well with BioMarin's clinical development experience in pediatric genetic disease and with the company's commercial development plans targeting genetic disease and pediatric specialists.

PKU is an inherited genetic disease in which initial treatment is focused primarily on children, similar to mucopolysaccharidosis I (MPS I) and mucopolysaccharidosis VI (MPS VI). BioMarin and joint venture partner Genzyme Corporation successfully developed Aldurazyme(R) for MPS I. BioMarin is currently conducting a Phase 3 trial of Aryplase(TM) for MPS VI and, pending positive results, plans to file a biologics license application in the fourth quarter of 2004. The company is currently evaluating strategies for commercializing Aryplase in the US and EU. With a partner or by itself, BioMarin could leverage a single US-based infrastructure focused on genetic and pediatric disease specialists to commercialize Aryplase, Phenoptin and Phenylase.

About PKU

PKU (phenylketonuria), a genetic disorder affecting at least 50,000 diagnosed patients under the age of 40 in the developed world, is caused by a deficiency of the enzyme, phenylalanine hydroxylase (PAH). PAH is required for the breakdown of phenylalanine (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 resulting in a variety of complications, including severe mental retardation and brain damage, mental illness, seizures and tremors, and cognitive problems. As a result of global newborn screening efforts implemented in the 1960s and early 1970s, virtually all PKU patients in developed countries have been diagnosed at birth. The only treatment currently available for PKU patients is a highly restrictive and expensive medical food diet that most patients find difficult to maintain.

Additional Information on BioMarin's PKU Program

The following questions and answers are intended to provide additional information regarding BioMarin's PKU program:

Question # 1 -- What is the size of the market opportunity for PKU?

Answer -- There are at least 50,000 people under the age of 40 in developed countries who have PKU. If approved, approximately 30 to 50 percent of this population could be treated with Phenoptin, an oral product, and the remainder could be treated with Phenylase, an injectable product. The theoretical market for medical foods, based on an annual cost of approximately $7,500 per patient, is $375,000,000. Although it is premature to discuss pricing for either Phenoptin or Phenylase, it is thought that the market size for PKU drug therapies could be equal to or greater than the potential size of the medical foods market.

Furthermore, in 2000, the NIH recommended lifelong treatment for all PKU patients underscoring the need for an alternative to a low-Phe medical food diet for management of PKU. Compliance with a low-Phe diet is difficult, especially during and beyond adolescence, and as well as for those who have been off a restricted diet for extended periods. Phenoptin taken orally, or Phenylase injected, aim to provide PKU patients with a treatment option that is efficacious, cost effective, and allows them to experience a less restrictive or normal diet.

Question # 2 -- What are the advantages of the Phenoptin manufacturing process that could enable efficient, lower cost development of the 6R form of tetrahydrobiopterin for PKU?

Answer -- Phenoptin is being manufactured using Merck Eprova's proprietary microcrystalline stabilization technology currently used to produce similar compounds, such as Metafolin(TM) and Leucovorin(TM), eliminating storage and distribution constraints.

Tetrahydrobiopterin produced through conventional methods can degrade quickly at room temperature and must be stored frozen which poses storage and distribution constraints. Historically, tetrahydrobiopterin has been very difficult and expensive to produce using a conventional manufacturing process that is based on technology developed over 20 years ago.

Question # 3 -- What percentage of PKU patients is likely to respond to Phenoptin?

Answer -- Studies to date indicate that 30 to 50 percent of PKU patients respond significantly to tetrahydrobiopterin. Responses have been most consistently observed in patients with moderate or mild forms of PKU. Available data suggest that a higher percentage of patients may respond favorably under different dosing regimens and with the second generation product. Many patients with the most severe form of PKU, characterized by the complete absence of active PAH, are unlikely to respond to Phenoptin, although some severe patients may respond to a lesser degree than those with the mild or moderate forms of PKU.

Question # 4 -- What percentage of patients has the most severe form of PKU, and why don't they respond to tetrahydrobiopterin?

Answer -- It is estimated that approximately 50 percent of PKU patients have the most severe type of the disease. The most likely reason that most patients in the severe subset may not respond to tetrahydrobiopterin as well as those with the mild to moderate forms is that their particular PAH mutations may completely prevent PAH enzyme synthesis preventing 'activation' of enzyme activity by its cofactor tetrahydrobiopterin.

Question # 5 -- Is BioMarin developing a product for patients with the most severe form of PKU?

Answer -- BioMarin is developing Phenylase, a recombinant form of the PAH enzyme acquired by BioMarin from IBEX in 2001. Phenylase is aimed at enzymatically eliminating Phe in the body, and could address the more severe forms of PKU. We are currently evaluating Phenylase as a subcutaneous injectable product in a PKU mouse model. To date, results have been positive and have demonstrated a dose-dependent reduction in blood Phe level into the appropriate control range for several days. BioMarin expects to complete proof-of-concept work in animal models in 2004, and if results are positive, begin clinical testing of Phenylase in 2005.

Question # 6 - What are the development plans for BioMarin's PKU program?

Answer -- BioMarin will support a clinical study of oral tetrahydrobiopterin in the first quarter of 2004 to evaluate the optimal method to screen for likely responders to Phenoptin. The aim of this study is to better define the population in which Phenoptin will be tested in subsequent clinical trials that are expected to begin in the second half of 2004.

Preclinical trials evaluating Phenylase dosing regimens and formulations in an animal model of PKU will be conducted in 2004. BioMarin will also be exploring the feasibility of a PEGylated (polyethylene glycol encapsulated) form of Phenylase to maintain reduced Phe levels for an extended period of time.

Additionally, BioMarin is building a database of diagnosed PKU patients. This information will be used to determine the most appropriate clinical trial designs and to prepare for the potential commercialization of

Phenoptin.

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BioMarin develops and commercializes enzyme-related therapies for serious, life-threatening diseases and conditions.

With more than 34,500 employees in 53 countries, the Merck Group generated sales of EUR 7.5 billion in 2002. Founded in 1668 in Darmstadt, Germany, the company aims to be a world leader within its core businesses of pharmaceuticals and chemicals. Merck groups its operating activities under Merck KGaA, in which the Merck family holds 74% and the remaining 26% is publicly traded. The former U.S. subsidiary, Merck & Co., has been a completely independent company since 1917.

Merck Eprova AG, based in Schaffhausen, Switzerland, is a fully-owned subsidiary of Merck KGaA and part of Merck's global custom synthesis and services network. For further information, please enter our website: www.merck-lsp.de.

Forward-Looking Statement

This press release contains forward-looking statements about the business prospects of BioMarin Pharmaceutical Inc., including, without limitation, statements about: expectations about preclinical and clinical development of Phenoptin, expectations about the manufacture and commercial development of, and actions of regulatory authorities with respect to, Phenoptin, including expected costs to develop and manufacture and sales of Phenoptin; the net loss and cash burn of BioMarin for fiscal years 2003 and 2004; expectations relating to the partnership with Merck Eprova; results and progress related to preclinical and clinical trials of Phenylase and Aryplase, including expected timing, progress, enrollment and conduct of current and future trials and the commercial development of such product candidates; and patient registry activities. 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 final analysis of results of past preclinical and clinical trials; results and timing of current and future preclinical and clinical trials; enrollment rates of current and future clinical trials; the content and timing of decisions by regulatory authorities; costs to develop, manufacture and sell products; and those factors detailed in BioMarin's filings with the Securities and Exchange Commission, including, without limitation, the factors contained under the caption "Factors That May Affect Future Results" in BioMarin's 2002 Annual Report on Form 10-K and the factors contained in BioMarin's reports on Forms 10-Q and 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's press releases and other company information are available online at http://www.bmrn.com/ . Information on BioMarin's website is not incorporated by reference into this press release.

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