PNAS Study from BioMarin Highlights Possible New Approach for Improving the Efficacy of Enzyme and Protein Replacement Therapies

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Patients receiving protein-based biopharmaceuticals may eventually benefit from a technology to improve their immune tolerance to such treatments, according to early stage research to be published this week in the Proceedings of the National Academy of Sciences (PNAS). The study, led by scientists at BioMarin Pharmaceutical Inc. , demonstrated a substantial reduction in the long-term immune response to specific enzyme replacement therapies in an animal model, without the continued use of immunosuppressive drugs. The immune response induced by certain protein-based drugs can reduce the efficacy and safety of treatment and is an increasingly common medical problem caused by the emergence of protein-based drugs used to treat chronic diseases.

"The work presented in PNAS is indicative of our innovative approach to developing and commercializing therapeutics for patients who suffer from enzyme deficiency and other genetic diseases," said Fredric D. Price, Chairman and Chief Executive Officer of BioMarin. "We are excited by these findings and the potential of this technology to enhance our pipeline of enzyme-based therapies as well as therapies for other, more prevalent diseases."

Background

Repeated administration of protein-based drugs can cause patients to develop neutralizing antibodies that bind to the drugs, remove them from circulation, and ultimately reduce their efficacy and cause adverse side effects. This

medical problem is becoming more common as an increasing number of new drugs to treat chronic conditions are protein-based and induce strong immune responses. For example, patients with the inherited genetic disease hemophilia A receive chronic infusions of factor VIII, a recombinant protein that restores normal clotting function and prevents internal bleeding that can lead to injury and death. As many as 20 percent of hemophilia A patients develop high levels of neutralizing antibodies (called 'inhibitors') that can make factor VIII therapy ineffective. Using the immune tolerance technology developed at BioMarin, it may be possible to reduce or prevent the formation of factor VIII inhibitors. BioMarin plans to evaluate its immune tolerance technology for hemophilia A as well as other enzyme or protein replacement therapies in which neutralizing antibodies interfere with biopharmaceutical treatment.

Summary of Study Results Presented in PNAS

The data published in PNAS demonstrate a substantial reduction in antibody response to recombinant human alpha-L-iduronidase (rhIDU), an enzyme that normally elicits a strong antibody response in the animal model used for these studies. When the animals were pretreated with a specific regimen of immunosuppressive agents in combination with low dose infusions of the 'high-uptake' form of rhIDU, the antibody response to therapeutic doses of rhIDU was reduced by approximately 37 fold compared to control animals and was maintained at a low level despite continuing weekly exposure to the enzyme. Antibody levels in the tolerized animals remained low for as long as six months while receiving weekly infusions of rhIDU. The toleragenic form of the iduronidase enzyme is the high-uptake form (containing mannose 6-phosphate markers) that increases uptake through the mannose 6-phospate receptors found on the surface of most cell types.

Key Findings from the Studies

-- The induction of long-term immune tolerance required both components of the regimen: the high-uptake rhIDU and the immunosuppressive agents

-- The immunosuppressive regimen required to induce tolerance was comprised of high doses of one common immunosuppressive drug, cyclosporin A, combined with azathioprine, for several weeks during initial exposure to the enzyme

-- The mannose 6-phosphate markers on the enzyme that enhance cellular uptake of the enzyme through the mannose 6-phospate receptors on cell surfaces were necessary for tolerance induction

-- The induced tolerance was antigen-specific and did not cause animals to become broadly immunosuppressed

-- The toleragenic effect was maintained for up to 2.5 years without drug exposure

"These early data provide significant insights into the induction of immune tolerance that are likely applicable to other enzyme replacement therapies and possibly to other biopharmaceuticals," said Emil D. Kakkis, M.D., Ph.D., Senior Vice President, Business Operations of BioMarin, and lead author on the PNAS study. "The ability to induce long-term antigen-specific tolerance in humans would represent a significant medical advance."

Dr. Kakkis continued, "Similar positive results were observed when evaluating this technology for inducing tolerance to alpha-glucosidase, another enzyme being studied as an enzyme replacement therapy to treat Pompe disease that previously exhibited an antibody response that may interfere with therapy(1). The data on which proteins were toleragenic suggest a strategy for the creation and administration of toleragenic versions of alpha- glucosidase and other

protein therapeutics, such as factor VIII, that could be important in the treatment of these and other more common disorders."

BioMarin has filed two patent applications related to the technology used in the study, which was originally supported by a grant from the National Institutes of Health and is being conducted through a collaborative research agreement with Harbor-UCLA Research and Education Institute. The company has an exclusive worldwide license to this technology and any intellectual property that results from this research.

The title of the study to be published in the online edition of PNAS prior to the printed edition is "Successful induction of immune tolerance to enzyme replacement therapy in canine mucopolysaccharidosis I" with the authors E. Kakkis, BioMarin Pharmaceutical Inc., Novato, CA; T. Lester, R. Yang, C. Tanaka, V. Anand, J. Lemontt, M. Peinovich, M. Passage, Division of Medical Genetics, Department of Pediatrics, Harbor-University of California at Los Angeles Research and Education Institute, Torrance, CA

The article will be available sometime during the week of December 29, 2003 in the PNAS Online Early Edition at www.pnas.org .

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

Forward-Looking Statement

This press release contains forward-looking statements about the business prospects of BioMarin Pharmaceutical Inc., including without limitation, statements about: current preclinical research related to immune tolerance regimen and expectations regarding further preclinical research in such

program. 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: actual results and timing of current and future preclinical trials; the results of possible future clinical trials related to the immune tolerance regimen; the content and timing of decisions by the United States Food and Drug Administration, the European Commission and other regulatory authorities; 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.

(1) Amalfitano et al Genet. Med. 2001, p132-138.

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