BIOMARIN PHARMACEUTICAL INC
Form 424B5
March 24, 2006
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Filed Pursuant to Rule 424(b)(5).

A filing fee of $18,457.50, calculated in accordance with

Rule 457(r), has been transmitted to the SEC in connection

with the securities offered from the registration statement

(File No. 333-132566) by means of this prospectus supplement.

PROSPECTUS SUPPLEMENT

(To Prospectus dated March 20, 2006)

$150,000,000

2.50% Senior Subordinated Convertible Notes due 2013

The Offering:

The notes will bear interest at the rate of 2.50% per year on the principal amount of the notes, payable in cash semiannually in arrears on September 29 and March 29 of each year, beginning September 29, 2006. The notes will mature on March 29, 2013. The notes will be our unsecured senior subordinated obligations and will rank junior in right of payment to our existing and future senior debt, equal in right of payment with our existing and future senior subordinated debt, and senior in right of payment to our existing and future subordinated debt. In addition, the notes will effectively rank junior in right of payment to all of our existing and future secured debt, to the extent of the value of the assets securing such debt, and to the debt and all other liabilities of our subsidiaries.

Convertibility of the Notes:

Holders may convert, at any time prior to maturity, any outstanding notes into shares of our common stock. The notes are convertible at a conversion rate of 60.3318 shares per $1,000 principal amount of notes, which is equal to a conversion price of approximately $16.58 per share, subject to adjustment. If a holder elects to convert notes in connection with a fundamental change, such holder may also be entitled to receive a make-whole premium upon conversion in certain circumstances. Our common stock is quoted on the Nasdaq National Market and traded on the SWX Swiss Exchange under the symbol BMRN . On March 23, 2006, the last sale price for our common stock as reported on the Nasdaq

National Market was $13.13 per share.

Purchase of the Notes at the Option of the Holder:

Upon a fundamental change of our company, each holder may require us to purchase all or a portion of such holder s notes at a price equal to the principal and accrued and unpaid interest, if any.

We are concurrently offering 9,000,000 shares, or 10,350,000 shares if the underwriters exercise their overallotment option in full, of our common stock pursuant to a separate prospectus supplement.

Investing in our notes involves risks, including those described in the Risk Factors section beginning on page S-8 of this prospectus supplement.

	Per Note	Total
Public offering price	$1,000	$150,000,000
Underwriting discount	$30	$4,500,000
Proceeds, before expenses, to us	$970	$145,500,000

We have granted the underwriter a 13-day option to purchase up to an additional $22,500,000 principal amount of notes to cover overallotments, if any.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus supplement or the accompanying prospectus is truthful or complete. Any representation to the contrary is a criminal offense.

The notes will be ready for delivery in book entry form only through the facilities of the Depositary Trust Company on or about March 29, 2006.

Merrill Lynch & Co.

The date of this prospectus supplement is March 23, 2006.

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Prospectus Supplement

You should rely only on the information contained or incorporated by reference in this prospectus supplement, the accompanying prospectus and the documents incorporated by reference therein. We have not, and the underwriter has not, authorized anyone to provide you with different information. If anyone provides you with different or inconsistent information, you should not rely on it. We are not, and the underwriter is not, making an offer to sell these securities in any jurisdiction where the offer or sale is not permitted. You should assume that the information appearing in this prospectus supplement, the accompanying prospectus and the documents incorporated by reference in this prospectus supplement and the accompanying prospectus is accurate only as of the date on those respective documents. Our business, financial condition, results of operations and prospects may have changed since those dates. You should read this prospectus supplement and the accompanying prospectus, including the documents incorporated by reference in this prospectus supplement and the accompanying prospectus, when making your investment decision. You should also read and consider the information in the documents we have referred you to in the sections of the prospectus entitled Where You Can Find More Information and Information Incorporated by Reference.

General information about us can be found on our website at http://www.BMRN.com . The information on our website is for information only and should not be relied on for investment purposes. The information on our website is not incorporated by reference into either this prospectus supplement or the accompanying prospectus and should not be considered part of this or any other report filed with the Securities and Exchange Commission.

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ABOUT THIS PROSPECTUS SUPPLEMENT

This prospectus supplement and the accompanying prospectus are part of a registration statement that we filed with the Securities and Exchange Commission (SEC), utilizing a shelf registration process. This prospectus supplement provides you with the specific details regarding this offering, including the principal amount, conversion ratio and ranking of our notes, and the risks of investing in our notes. The accompanying prospectus provides you with more general information, some of which does not apply to the offering of our notes. To the extent information in this prospectus supplement is inconsistent with the accompanying prospectus or any of the documents incorporated by reference into this prospectus supplement and the accompanying prospectus, you should rely on this prospectus supplement. You should read and consider the information in both this prospectus supplement and the accompanying prospectus together with the additional information described under the headings Where You Can Find More Information and Information Incorporated by Reference .

This prospectus supplement and the accompanying prospectus have not been approved by the Financial Services Authority. The notes may not be offered or sold to any person in the United Kingdom except where the offer is exempt from the general prohibition against the offer of securities to the public under section 85 of the Financial Services and Markets Act 2000 (FMSA) by virtue of one or more of the criteria set out in section 86 of FMSA.

This prospectus supplement and the accompanying prospectus is directed only at (i) persons outside the United Kingdom, (ii) persons who have professional experience in matters relating to investments and who are investment professionals within the meaning of Article 19(5) of FMSA (Financial Promotion) Order 2005 of the United Kingdom (the Financial Promotion Order), (iii) persons who fall within Article 49(2)(a) through (d) (high net worth companies, unincorporated associations, etc.) of the Financial Promotion Order, or (iv) any other persons to whom this prospectus supplement and the accompanying prospectus for the purposes of Section 21 of FSMA can otherwise lawfully be made (all such persons together being referred to as Relevant Persons), and must not be acted on or relied upon by persons other than Relevant Persons.

NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus supplement, the accompanying prospectus and the documents incorporated by reference in this prospectus supplement and the accompanying prospectus contain forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, included in this prospectus, the prospectus supplement or any document incorporated by reference in this prospectus or any prospectus supplement regarding our strategy, future operations, future financial position, future revenues, projected costs, prospects and plans and objectives of management are forward-looking statements.

Forward-looking statements include, but are not limited to, statements about:

- our expectations with respect to regulatory submissions and approvals and our clinical trials;
- our expectations with respect to our collaborations with Serono S.A. (Serono) and Genzyme Corporation (Genzyme); and
- our estimates regarding our capital requirements and our need for additional financing.

The words anticipates , believes , estimates , expects , intends , may , plans , projects , will , would and similar expressions are inte forward-looking statements, although not all forward-looking statements contain these identifying words. We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements that we make. We have identified some of the important factors that could cause future events to materially differ from our current expectations and they are described in this prospectus supplement under the caption Risk Factors as well as in our most recent Annual Report on Form 10-K. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures or investments we may make. We do not assume any obligation to update any forward-looking statement.

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PROSPECTUS SUPPLEMENT SUMMARY

This summary highlights selected information contained elsewhere or incorporated by reference in this prospectus supplement. This summary does not contain all the information that you should consider before investing in our notes. You should read the entire prospectus supplement and the accompanying prospectus carefully, including Risk Factors , the financial statements and other information included or incorporated by reference in this prospectus supplement and the accompanying prospectus before making an investment decision. This prospectus supplement contains forward-looking statements that involve risks and uncertainties. Our actual results could differ materially from the results anticipated in these forward-looking statements as a result of factors described under the Risk Factors section and elsewhere in this prospectus supplement. Unless the context otherwise requires, any reference to BioMarin, we, our and us in this prospectus supplement refers to BioMarin Pharmaceutical Inc., and its subsidiaries.

BioMarin Pharmaceutical Inc.

Overview

We develop and commercialize innovative biopharmaceuticals for serious diseases and medical conditions. We select product candidates for diseases and conditions that represent a significant unmet medical need, have well-understood biology and provide an opportunity to be first-to-market. Our product portfolio is comprised of two approved products and multiple investigational product candidates. Approved products include Aldurazyme® (laronidase) and Naglazyme (galsulfase). Additionally, we have rights to receive payments and royalties related to Orapred® (see Recent Developments Orapred License Agreement).

Marketed Products

Aldurazyme

Aldurazyme has been approved for marketing in the United States (U.S.) by the U.S. Food and Drug Administration (FDA), in the European Union (E.U.) by the European Commission (EC) and in other countries for the treatment of mucopolysaccharidosis I (MPS I), for which no other drug treatment currently exists. MPS I is a progressive and debilitating life-threatening genetic disease, which frequently results in death during childhood or early adulthood. It is caused by the deficiency of alpha-L-iduronidase, an enzyme normally required for the breakdown of certain complex carbohydrates known as glycosaminoglycans (GAGs). Aldurazyme has been granted orphan drug exclusivity in the U.S. and the E.U., which gives Aldurazyme seven years of market exclusivity in the U.S. and 10 years of market exclusivity in the E.U. for the treatment of MPS I, expiring in 2010 and 2013, respectively. We developed Aldurazyme through a 50/50 joint venture with Genzyme. Aldurazyme net revenue recorded by our joint venture for 2005 totaled $76.4 million, compared to $42.6 million for 2004.

Naglazyme

In May 2005, the FDA granted marketing approval for Naglazyme for the treatment of mucopolysaccharidosis VI (MPS VI), a debilitating life-threatening genetic disease for which no other drug treatment currently exists. MPS VI is caused by the deficiency of N-acetylgalactosamine 4-sulfatase (arylsulfatase B), an enzyme normally required for the breakdown of GAGs. Naglazyme net product sales recorded for 2005 totaled $6.1 million. In January 2006, the EC granted marketing approval for Naglazyme in the E.U. Naglazyme has been granted orphan drug exclusivity in the U.S. and the E.U., which gives Naglazyme seven years of market exclusivity in the U.S. and 10 years of market exclusivity in the E.U. for the treatment of MPS VI, expiring in 2012 and 2016, respectively. Product launch in the E.U. is underway on a country-by-country basis.

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Products in Development

We are developing several investigational product candidates for the treatment of genetic diseases including: Phenoptin (sapropterin dihydrochloride), a proprietary oral form of tetrahydrobiopterin (6R-BH_4, also commonly referred to as BH_4), for the treatment of phenylketonuria (PKU); and Phenylase (phenylalanine ammonia lyase), an enzyme substitution therapy for the treatment of phenylketonurics who are not 6R-BH_4-responsive.

Phenoptin

In December 2004, we announced that we initiated our Phase 2 clinical trial of Phenoptin for PKU. Patients enrolled in the Phase 2 clinical trial who met certain criteria were eligible to enroll in the Phase 3 clinical trial, which began in April 2005. The Phase 3 clinical trial of Phenoptin was a six-week, multi-center, international, double-blind, placebo-controlled study. On March 15, 2006, we announced positive results from the Phase 3 clinical trial (see Recent Developments Phase 3 Phenoptin Data). We also plan to conduct a supplemental diet study in children between 4 to 12 years of age. We have received orphan drug designation for Phenoptin for the treatment of PKU in both the U.S. and E.U. If Phenoptin is approved for marketing, it will have seven years of market exclusivity in the U.S. and ten years of market exclusivity in the E.U. In January 2006, the FDA designated Phenoptin as a fast-track product for the treatment of PKU.

PKU is an inherited metabolic disease that affects at least 50,000 diagnosed patients under the age of 40 in the developed world. We believe that 30% to 50% of those with PKU could benefit from treatment with Phenoptin, if approved. PKU is caused by a deficiency of an enzyme, phenylalanine hydroxylase (PAH), which is required for the metabolism of Phenylalanine (Phe). Phe is an amino acid found in protein-containing foods. Without sufficient quantity or activity of PAH, Phe accumulates to abnormally high levels in the blood resulting in a variety of serious neurological complications. Currently, the only way to manage PKU is through an extremely restricted diet that patients find very difficult to follow. Phenoptin, our lead product candidate for the treatment of PKU, is a proprietary, synthetic oral form of 6R-BH_4, a small-molecule therapeutic that is a co-factor for PAH. If approved, Phenoptin could become the first drug for the treatment of PKU.

In May 2005, the Company entered into an agreement with Serono for the further development and commercialization of Phenoptin and Phenylase for PKU, and 6R-BH_4, the active ingredient in Phenoptin, for other diseases including those associated with endothelial dysfunction. Through the agreement, Serono acquired exclusive rights to market these products in all territories outside the U.S. and Japan, and BioMarin retained exclusive rights to market these products in the U.S. BioMarin and Serono will generally share equally all development costs following successful completion of Phase 2 clinical trials for each product candidate in each indication. BioMarin and Serono are individually responsible for the costs of commercializing the products within their respective territories. Serono will also pay BioMarin royalties on its net sales of these products and milestone payments for the successful completion of certain development and approval milestones.

Endothelial dysfunction is a condition characterized by the inability of the endothelium (the single cell layer lining that forms the barrier between blood vessel walls and the blood) to respond to physiological changes correctly. In preclinical and investigator-sponsored studies, BH_4 administration has improved vascular endothelial function in animal models and in patients with diabetes and other cardiovascular diseases. BH_4 is a naturally occurring enzyme cofactor required for the production of nitric oxide, a molecule that is key to the regulation of dilation and constriction of blood vessels. We plan to conduct additional preclinical and clinical studies of BH_4 for endothelial dysfunction in 2006.

Other Programs

We are evaluating other therapies for serious medical conditions including Phenylase and Vibrilase (vibriolysin).

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Phenylase is an investigational enzyme substitution therapy currently in preclinical development. It is being developed as a subcutaneous injection and is intended for those who suffer from classic PKU and for those who are not 6R-BH_4 responsive, and do not respond to Phenoptin.

Vibrilase is an investigational topical enzyme therapy for use in the debridement of serious burns. In August 2004, we announced positive data from a Phase 1b clinical trial of Vibrilase. Data from the trial suggest that treatment with Vibrilase is generally safe and well-tolerated. Additionally, we are evaluating preclinical development of several other enzyme product candidates for genetic and other diseases as well as an immune tolerance platform technology designed to overcome limitations associated with the delivery of existing pharmaceuticals.

Recent Developments

Phase 3 Phenoptin Data

On March 15, 2006, Serono and we announced positive results of a Phase 3, double-blind, placebo-controlled clinical study of Phenoptin for the treatment for PKU. Results confirmed that all pre-specified primary and secondary endpoints were met and data from the Phase 3 study demonstrate a statistically significant reduction at six weeks in blood Phe levels in patients receiving Phenoptin, compared with those receiving placebo.

Following the six-week double-blind study, patients were eligible to enroll into an on-going 22 week Phase 3 open-label extension study designed to further evaluate the long-term safety and efficacy of Phenoptin, as well as dose titration. Serono and we expect to file marketing authorization applications for Phenoptin for PKU in the U.S. and E.U. in 2007. We have licensed to Serono exclusive rights for Phenoptin outside of the U.S. and Japan.

The Phase 3 study enrolled 89 patients with elevated blood Phe levels aged eight years and above at 29 sites in the U.S., Europe and Canada. All patients demonstrated a reduction in blood Phe levels (approximately 30% or more) following treatment with Phenoptin in a Phase 2 screening study.

The patients were randomly assigned to receive placebo or 10 mg/kg of Phenoptin daily for six weeks. Patients were evaluated every two weeks for changes in blood Phe levels and adverse events. The primary endpoint of the study was the difference in mean blood Phe levels between the placebo and Phenoptin groups at Week 6, adjusted for baseline levels. A total of 87 patients completed six weeks of treatment.

Results from the Phase 3 double-blind study are summarized below:

Primary Endpoint

Patients treated with Phenoptin for six weeks had a mean decrease in blood Phe level of 236 μM (29%) compared to an increase of 3 μM (3%) in the placebo group ($p<0.0001$). Prior to treatment, patients in the Phenoptin group and placebo group had mean blood Phe levels of 843 μM and 888 μM, respectively.

Secondary Endpoints

At Week 6, the percentage of patients in the Phenoptin group with blood Phe levels less than or equal to 600 μM was 54% compared to 23% in the placebo group ($p=0.004$). At baseline the proportions were 17% and 19% for the Phenoptin and placebo groups, respectively.

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The mean blood Phe level at each visit among patients receiving Phenoptin showed a consistent reduction compared to the blood Phe levels in patients receiving placebo ($p<0.001$) throughout the six-week period.

The type and incidence of adverse events was similar in the Phenoptin and placebo groups. Phenoptin was generally well tolerated and investigators reported no serious adverse events occurred.

Orapred License Agreement

On March 15, 2006, we entered into an agreement with Alliant Pharmaceuticals (Alliant) pursuant to which we licensed to Alliant exclusive North American rights to the Orapred (prednisolone sodium phosphate oral solution) product line, including Orapred ODT (prednisolone sodium phosphate orally disintegrating tablets).

Under the terms of the agreement, Alliant paid us $2.5 million upon signing of the definitive agreement and will make milestone payments of up to $15.5 million contingent primarily on the approval and commercial launch of Orapred ODT in the U.S., both of which are anticipated to occur in the second half of 2006. Upon approval and commercial launch of Orapred ODT in the U.S., we will be required to make milestone payments of $3.2 million to a third party. Alliant will pay us royalties ranging from 25% to 30% on net sales of Orapred ODT, net of royalties owed to a third party, in exchange for the exclusive rights to commercialize Orapred products in North America. We have retained commercial rights outside of North America.

Net sales of Orapred, including the branded and authorized generic products, for the 12 months ended December 31, 2005 were $6.9 million.

Orapred ODT, a new formulation of Orapred currently under review by the FDA, utilizes a proprietary orally disintegrating tablet technology to provide a taste-masked, non-refrigerated and easy-to-administer formulation of prednisolone. In August 2005, we filed a New Drug Application for Orapred ODT with the FDA. Pursuant to the Prescription Drug User Fee Act, we expect that the FDA will take action on the application by June 1, 2006. If approved, Orapred would be the first orally disintegrating tablet corticosteroid dosage form available in the U.S.

Company Information

Our principal executive offices are located at 105 Digital Drive, Novato, California 94949 and our telephone number is (415) 506-6700. BioMarin, Naglazyme, Phenoptin, Vibrilase, and Phenylase are our trademarks. Aldurazyme is a registered trademark of BioMarin/Genzy LLC. Orapred is a registered trademark of Medicis Pediatrics, Inc., and is used under license. All other service marks and all brand names or trademarks appearing in this prospectus supplement and the accompanying prospectus are the property of their respective holders.

Concurrent Common Stock Offering

Concurrently with this offering of notes, we are offering 9,000,000 shares, or 10,350,000 shares if the underwriters exercise their overallotment option in full, of common stock to the public, which we refer to herein as the common stock offering. The common stock offering is being conducted as a separate public offering by means of a separate prospectus supplement. This offering is not contingent upon the common stock

offering, and the common stock offering is not contingent upon this offering.

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THE OFFERING

The following is a brief summary of the terms of this offering. For a complete description of the terms of the notes, see Description of the Notes in this prospectus supplement.

Issuer	BioMarin Pharmaceutical Inc.
Notes to be offered	$150,000,000 aggregate principal amount, or $172,500,000 if the underwriter exercises its option to purchase additional notes in full, of senior subordinated convertible notes due 2013.
Maturity date	March 29, 2013.
Interest and payment dates	2.50% per year on the principal amount, payable semiannually in arrears in cash on September 29 and March 29 of each year, beginning September 29, 2006.
Conversion rights	The notes are convertible, at the option of the holder, at any time on or prior to maturity, into shares of our common stock at a conversion rate of 60.3318 shares per $1,000 principal amount of notes per share, which is equal to a conversion price of approximately $16.58 per share. The conversion rate is subject to adjustment.
Make-whole premium upon a fundamental change	If a fundamental change (as described in this prospectus supplement) occurs, other than a fundamental change described under the third bullet point under the definition of a change in control described below under Description of the Notes Repurchase at Option of Holders Upon a Fundamental Change, we will pay a make-whole premium on notes converted in connection with a fundamental change by increasing the conversion rate on such notes. The amount of the make-whole premium, if any, will be based on our common stock price and the effective date of the fundamental change. A description of how the make-whole premium will be determined and a table showing the make-whole premium that would apply at various common stock prices and fundamental change effective dates is set forth under Description of the Notes Make-Whole Premium Upon a Fundamental Change.
Repurchase of notes by us at the option of the holders upon a fundamental change	If we undergo a fundamental change, except in certain circumstances, each holder will have the option to require us to repurchase all or any portion of such holder s notes. The fundamental change repurchase price will be 100% of the principal amount of the notes to be repurchased plus accrued and unpaid interest, if any.
Ranking	The notes will be unsecured and rank subordinated to our existing and future senior debt, equally with our existing and future senior

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	subordinated debt, and senior to our existing and future subordinated debt, including without limitation, our 3.50% convertible subordinated notes due 2008. As of March 14, 2006, we had $113.0 million in senior debt outstanding and $125.0 million 3.50% convertible subordinated notes due 2008, which will rank junior to the notes. Because the notes will be subordinated to our existing and future senior debt, in the event of bankruptcy, liquidation, dissolution or acceleration of payment on the senior debt, holders of the notes will not receive any payment until holders of the senior debt have been paid in full. The indenture under which the notes will be issued will not prevent us or our subsidiaries from incurring additional senior debt or other obligations.
Use of proceeds	We intend to apply the net proceeds of this offering and of the concurrent offering of common stock described above towards the commercialization of our products; additional clinical trials of Phenoptin, BH_4 for other indications, Phenylase and Vibrilase; preclinical studies and clinical trials for our other product candidates; potential licenses and acquisitions of complementary technologies, products and companies; general corporate purposes, including acquisition costs related to the purchase of our facility located at 46 Galli Drive for which we are currently under contract; and working capital. We may also use a portion of proceeds of these offerings to purchase some or all of our 3.50% convertible subordinated notes due 2008 pursuant to the redemption provisions of the indenture governing such notes whereby we have the right to call the notes beginning June 20, 2006, or in one or more privately negotiated transactions from time to time. This offering is not contingent on the concurrent common stock offering. See Use of Proceeds.
Form and denomination	The notes will be issued in minimum denominations of $1,000 and any integral multiple of $1,000.
Trading	The notes will not be listed on any securities exchange or included in any automated quotation system. The notes will be new securities for which there is currently no public market.
Nasdaq symbol for common stock	Our common stock is quoted on the Nasdaq National Market and traded on the SWX Swiss Exchange under the symbol BMRN .
Material U.S. federal income tax considerations	The notes and the shares of our common stock issuable upon conversion of the notes will be subject to special and complex U.S. federal income tax rules. Holders are encouraged to consult their tax advisors as to the U.S. federal, state, local or other tax consequences of acquiring, owning and disposing of the notes.
Risk factors	See Risk Factors and other information included in this prospectus supplement, the accompanying prospectus and the documents incorporated by reference in this prospectus supplement and the accompanying prospectus for a discussion of factors you should carefully consider before deciding to invest in shares of our notes.

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RISK FACTORS

An investment in our notes involves a high degree of risk. We operate in a dynamic and rapidly changing industry that involves numerous risks and uncertainties. You should carefully consider the following risk factors, together with all of the other information contained in this prospectus supplement and the accompanying prospectus or incorporated by reference into this prospectus supplement and the accompanying prospectus. The risks and uncertainties described below are not the only ones we face. Other risks and uncertainties, including those that we do not currently consider material, may impair our business. If any of the risks discussed below actually occur, our business, financial condition, operating results or cash flows could be materially adversely affected. This could cause the value of our notes to decline, and you may lose all or part of your investment.

Risks Related to Our Business

If we continue to incur operating losses for a period longer than anticipated, we may be unable to continue our operations at planned levels and be forced to reduce or discontinue operations.

Since we began operations in March 1997, we have been engaged primarily in research and development and have operated at a net loss for the entire time. Our first product, Aldurazyme, was approved for commercial sale in the U.S. and the E.U. and has generated approximately $130.5 million in net sales revenue to our joint venture from the product s launch in May 2003 through December 31, 2005. We acquired exclusive rights to Orapred in May 2004 and reported $25.5 million in Orapred net product sales following the acquisition through December 31, 2005. On June 1, 2005 we announced that the FDA granted marketing approval for Naglazyme for the treatment of MPS VI. We reported $6.1 million in Naglazyme net product sales during 2005. We have no revenues from sales of our product candidates. As of December 31, 2005, we had an accumulated deficit of $563.1 million. We expect to continue to operate at a net loss for the foreseeable future. Our future profitability depends on our marketing and selling of Naglazyme, the successful commercialization of Aldurazyme by our joint venture partner, Genzyme, the amount of royalties we receive from our license of Orapred, the receipt of regulatory approval of our product candidates and our ability to successfully manufacture and market any approved drugs, either by ourselves or jointly with others. The extent of our future losses and the timing of profitability are highly uncertain. If we fail to become profitable or are unable to sustain profitability on a continuing basis, then we may be unable to continue our operations at planned levels and be forced to reduce or discontinue operations.

If we fail to obtain the capital necessary to fund our operations, our financial results and financial condition will be adversely affected and we will have to delay or terminate some or all of our product development programs.

We will require additional financing to fund our future operations, including the commercialization of our approved drugs and drug product candidates currently under development, preclinical studies and clinical trials, and potential licenses and acquisitions. We may be unable to raise additional financing when needed due to a variety of factors, including our financial condition, the status of our product programs, and the general condition of the financial markets. If we fail to raise additional financing as we need such funds, we will have to delay or terminate some or all of our product development programs and our financial condition and operating results will be adversely affected.

We expect to continue to spend substantial amounts of capital for our operations for the foreseeable future. The amount of capital we will need depends on many factors, including:

our ability to successfully market and sell Naglazyme;

our joint venture partner s ability to successfully commercialize Aldurazyme;

the progress, timing and scope of our preclinical studies and clinical trials;

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- the amount of royalties we receive from our license of Orapred;
- the time and cost necessary to obtain regulatory approvals and the costs of post-marketing studies which may be required by regulatory authorities;
- the time and cost necessary to develop commercial manufacturing processes, including quality systems, and to build or acquire manufacturing capabilities;
- our ability to maintain compliance with our debt covenants;
- the time and cost necessary to respond to technological and market developments;
- any changes made or new developments in our existing collaborative, licensing and other commercial relationships or any new collaborative, licensing and other commercial relationships that we may establish; and
- whether our convertible debt is converted to common stock in the future.

Moreover, our fixed expenses such as rent, license payments, interest expense and other contractual commitments are substantial and will increase in the future. These fixed expenses will increase because we expect to enter into:

- additional licenses and collaborative agreements;
- additional contracts for consulting, maintenance and administrative services;
- additional contracts for product manufacturing; and
- additional financing facilities.

We believe that our cash, cash equivalents, short-term investment securities and cash balances related to long-term debt at December 31, 2005, plus funds contractually committed to us will be sufficient to meet our operating and capital requirements into the first quarter of 2007. These estimates are based on assumptions and estimates, including the availability of a $25.0 million loan from Medicis. These assumptions and estimates may prove to be wrong. Additionally, we are required to maintain a total unrestricted cash balance of at least $25.0 million under our credit facility with Comerica. We will need to sell equity or debt securities to raise additional funds if we are unable to satisfy our liquidity requirements. The sale of additional securities may result in additional dilution to our stockholders. Furthermore, additional financing may not be available in amounts or on terms satisfactory to us or at all. This could result in the delay, reduction or termination of our research, which could harm our business.

If we fail to maintain regulatory approval to commercially market or sell our drugs, or if approval is delayed, we will be unable to generate revenue from the sale of these products, our potential for generating positive cash flow will be diminished, and the capital necessary to fund our operations will be increased.

We must obtain regulatory approval before marketing or selling our drug products in the U.S. and in foreign jurisdictions. In the U.S., we must obtain FDA approval for each drug that we intend to commercialize. The FDA approval process is typically lengthy and expensive, and approval is never certain. Products distributed abroad are also subject to foreign government regulation. Aldurazyme, Naglazyme and Orapred have received regulatory approval to be commercially marketed and sold in the U.S., and Aldurazyme and Naglazyme have received regulatory approval to be commercially marketed and sold in the E.U. and other countries. If we fail to obtain regulatory approval for our other product candidates, we will be unable to market and sell those drug products. Because of the risks and uncertainties in pharmaceutical development, our product candidates could take a significantly longer time to gain regulatory approval than we expect or may never gain approval.

From time to time during the regulatory approval process for our products and our product candidates, we engage in discussions with the FDA and foreign regulatory authorities regarding the regulatory requirements

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of our development programs. To the extent appropriate, we accommodate the requests of the regulatory authorities and, to date, we have generally been able to reach reasonable accommodations and resolutions regarding the underlying issues. However, we are often unable to determine the outcome of such deliberations until they are final. If we are unable to effectively and efficiently resolve and comply with the inquiries and requests of the FDA and foreign regulatory authorities, the approval of our product candidates may be delayed and their value may be reduced.

After any of our products receive regulatory approval, they remain subject to ongoing FDA regulation, including, for example, changes to the product labeling, new or revised regulatory requirements for manufacturing practices and reporting adverse reactions and other information. If we do not comply with the FDA s regulations, the range of possible sanctions includes FDA issuance of adverse publicity, product recalls or seizures, fines, total or partial suspensions of production and/or distribution, suspension of FDA s review of marketing applications, enforcement actions, including injunctions and civil or criminal prosecution. The FDA can withdraw a product s approval under some circumstances, such as the failure to comply with existing or future regulatory requirements or unexpected safety issues. Further, the FDA may condition approval of our product candidates on the completion of additional post-marketing clinical studies. These post-marketing studies may suggest that a product causes undesirable side effects or may present a risk to safety. If data we collect from post-marketing studies suggest that one of our approved products may present a risk to safety, the FDA could withdraw our product approval, suspend production or place other marketing restrictions on our products. If regulatory sanctions are applied or if regulatory approval is delayed or withdrawn, our management s credibility, the value of our company and our operating results will be adversely affected. Additionally, we will be unable to generate revenue from the sale of these products, our potential for generating positive cash flow will be diminished and the capital necessary to fund our operations will be increased.

To obtain regulatory approval to market our products, preclinical studies and costly and lengthy preclinical and clinical trials are required and the results of the studies and trials are highly uncertain.

As part of the regulatory approval process, we must conduct, at our own expense, preclinical studies in the laboratory on animals and clinical trials on humans for each product candidate. We expect the number of preclinical studies and clinical trials that the regulatory authorities will require will vary depending on the product candidate, the disease or condition the drug is being developed to address and regulations applicable to the particular drug. We may need to perform multiple preclinical studies using various doses and formulations before we can begin clinical trials, which could result in delays in our ability to market any of our product candidates. Furthermore, even if we obtain favorable results in preclinical studies on animals, the results in humans may be significantly different. After we have conducted preclinical studies in animals, we must demonstrate that our drug products are safe and efficacious for use in the targeted human patients in order to receive regulatory approval for commercial sale.

Adverse or inconclusive clinical results would stop us from filing for regulatory approval of our product candidates. Additional factors that can cause delay or termination of our clinical trials include:

- slow or insufficient patient enrollment;
- slow recruitment of, and completion of necessary institutional approvals at, clinical sites;
- longer treatment time required to demonstrate efficacy;
- lack of sufficient supplies of the product candidate;

adverse medical events or side effects in treated patients;

lack of effectiveness of the product candidate being tested; and

regulatory requests for additional clinical trials.

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Typically, if a drug product is intended to treat a chronic disease, as is the case with some of our product candidates, safety and efficacy data must be gathered over an extended period of time, which can range from six months to three years or more.

The fast-track designation for our product candidates, if obtained, may not actually lead to a faster review process and a delay in the review process or in the approval of our products will delay revenue from the sale of the products and will increase the capital necessary to fund these programs.

Our product candidates may not receive fast-track designation or a six-month review timeframe. Even with fast-track designation, it is not guaranteed that the total review process will be faster or that approval will be obtained, if at all, earlier than would be the case if the product had not received fast-track designation.

If we fail to comply with manufacturing regulations, our financial results and financial condition will be adversely affected.

Before we can begin commercial manufacture of our products, we must obtain regulatory approval of our manufacturing facilities, processes and quality systems; and the manufacture of our drugs must comply with GMP regulations. The GMP regulations govern facility compliance, quality control and documentation policies and procedures. In addition, our manufacturing facilities are continuously subject to inspection by the FDA, the State of California and foreign regulatory authorities, before and after product approval. Our manufacturing facility in Novato, California (Galli Drive) and GMP warehouse facilities have been inspected and licensed by the State of California for clinical pharmaceutical manufacture and have been approved by the FDA, the EC and health agencies in other countries for the commercial manufacture of Aldurazyme and by the FDA and EC for the commercial manufacture of Naglazyme. We have entered into contracts with third-party manufacturers to produce Orapred and Phenoptin.

Due to the complexity of the processes used to manufacture Aldurazyme, Naglazyme and our product candidates, we may be unable to continue to pass or initially pass federal or international regulatory inspections in a cost effective manner. For the same reason, any potential third-party manufacturer of Aldurazyme, Naglazyme or our product candidates may be unable to comply with GMP regulations in a cost effective manner. As anticipated by GMP requirements, manufacturing deviations and deviations from GMP can and do occur from time to time. When a deviation occurs, we take corrective actions, which may not always be successful. Continued or extensive deviations can cause a manufacturing facility to be out of compliance with GMP. If we, or our third-party manufacturers with whom we contract, are unable to comply with manufacturing regulations, we may be subject to fines, unanticipated compliance expenses, recall or seizure of our products, total or partial suspension of production and/or enforcement actions, including injunctions, and criminal or civil prosecution. These possible sanctions would adversely affect our financial results and financial condition.

If we fail to obtain or maintain orphan drug exclusivity for some of our products, our competitors may sell products to treat the same conditions and our revenues will be reduced.

As part of our business strategy, we intend to develop some drugs that may be eligible for FDA and E.U. orphan drug designation. Under the Orphan Drug Act, the FDA may designate a product as an orphan drug if it is a drug intended to treat a rare disease or condition, defined as a patient population of less than 200,000 in the U.S. The company that first obtains FDA approval for a designated orphan drug for a given rare disease receives marketing exclusivity for use of that drug for the stated condition for a period of seven years. Orphan drug exclusive marketing rights may be lost if the FDA later determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the drug. Similar regulations are available in the E.U. with a 10-year period of market exclusivity.

Because the extent and scope of patent protection for some of our drug products is particularly limited, orphan drug designation is especially important for our products that are eligible for orphan drug designation. For

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eligible drugs, we plan to rely on the exclusivity period under the Orphan Drug Act to maintain a competitive position. If we do not obtain orphan drug exclusivity for our drug products that do not have patent protection, our competitors may then sell the same drug to treat the same condition and our revenues will be reduced.

Even though we have obtained orphan drug designation for certain of our product candidates and even if we obtain orphan drug designation for our future product candidates, due to the uncertainties associated with developing pharmaceutical products, we may not be the first to obtain marketing approval for any orphan indication. Further, even if we obtain orphan drug exclusivity for a product, that exclusivity may not effectively protect the product from competition because different drugs can be approved for the same condition. Even after an orphan drug is approved, the FDA can subsequently approve the same drug for the same condition if the FDA concludes that the later drug is safer, more effective or makes a major contribution to patient care. Orphan drug designation neither shortens the development time or regulatory review time of a drug, nor gives the drug any advantage in the regulatory review or approval process.

Because the target patient populations for some of our products are small, we must achieve significant market share and obtain high per-patient prices for our products to achieve profitability.

Aldurazyme and Naglazyme both target diseases with small patient populations. As a result, our per-patient prices must be relatively high in order to recover our development costs and achieve profitability. Aldurazyme targets patients with MPS I and Naglazyme targets patients with MPS VI. We believe that we will need to market worldwide to achieve significant market penetration of each product. In addition, we are developing other drug candidates to treat conditions, such as other genetic diseases, with small patient populations. Due to the expected costs of treatment for Aldurazyme and Naglazyme, we may be unable to maintain or obtain sufficient market share for Aldurazyme or Naglazyme at a price high enough to justify our product development efforts.

If we are found in violation of federal or state fraud and abuse laws, we may be required to pay a penalty or be suspended from participation in federal or state health care programs, which may adversely affect our business, financial condition and results of operation.

We are subject to various federal and state health care fraud and abuse laws, including antikickback laws, false claims laws and laws related to ensuring compliance. The federal health care program antikickback statute makes it illegal for any person, including a pharmaceutical company, to knowingly and willfully offer, solicit, pay or receive any remuneration, directly or indirectly, in exchange for or to induce the referral of business, including the purchase, order or prescription of a particular drug, for which payment may be made under federal health care programs, such as Medicare and Medicaid. Under federal government regulations, certain arrangements (safe harbors) are deemed not to violate the federal antikickback statute. We seek to comply with these safe harbors. False claims laws prohibit anyone from knowingly and willfully presenting or causing to be presented for payment to third party payers (including government payers) claims for reimbursed drugs or services that are false or fraudulent, claims for items or services that were not provided as claimed, or claims for medically unnecessary items or services. Other cases have been brought under false claims laws alleging that off-label promotion of pharmaceutical products has resulted in the submission of false claims to government health care programs. Under the Health Insurance Portability and Accountability Act of 1996, we also are prohibited from knowingly and willfully executing a scheme to defraud any health care benefit program, including private payers, or knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for health care benefits, items or services. Violations of fraud and abuse laws may be punishable by criminal and/or civil sanctions, including fines and/or exclusion or suspension from federal and state health care programs such as Medicare and Medicaid.

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Many states have adopted laws similar to the federal antikickback statute, some of which apply to referral of patients for health care services reimbursed by any source, not just governmental payers. In addition, California passed a law that requires pharmaceutical companies to comply with both the April 2003 Office of Inspector General Compliance Program Guidance for Pharmaceutical Manufacturers and the July 2002 PhRMA Code on Interactions with Healthcare Professionals.

Neither the government nor the courts have provided definitive guidance on the application of these laws to our business. Law enforcement authorities are increasingly focused on enforcing these laws, and it is possible that some of our practices may be challenged under these laws. While we believe we have structured our business arrangements to comply with these laws, it is possible that the government could allege violations of, or convict us of violating, these laws. If we are found in violation of one of these laws, are required to pay a penalty or are suspended or excluded from participation in federal or state health care programs, our business, financial condition and results of operation may be adversely affected.

If we fail to obtain an adequate level of reimbursement for our drug products by third-party payers, the sales of our drugs would be adversely affected or there may be no commercially viable markets for our products.

The course of treatment for patients using Aldurazyme and Naglazyme is expensive. We expect patients to need treatment throughout their lifetimes. We expect that most families of patients will not be capable of paying for this treatment themselves. There will be no commercially viable market for Aldurazyme or Naglazyme without reimbursement from third-party payers. Additionally, even if there is a commercially viable market, if the level of reimbursement is below our expectations, our revenue and gross margins will be adversely affected.

Third-party payers, such as government or private health care insurers, carefully review and increasingly challenge the prices charged for drugs. Reimbursement rates from private companies vary depending on the third-party payer, the insurance plan and other factors. Reimbursement systems in international markets vary significantly by country and by region, and reimbursement approvals must be obtained on a country-by-country basis.

We currently have limited expertise in obtaining reimbursement. We rely on the expertise of our joint venture partner, Genzyme, to obtain reimbursement for the costs of Aldurazyme. We are developing our own reimbursement capabilities for Naglazyme and have initiated the process for obtaining reimbursement in the E.U. Reimbursement in the E.U. must be negotiated on a country-by-country basis and in many countries the product cannot be commercially launched until reimbursement is approved. The negotiation process in some countries can exceed 12 months. For our future products and for Naglazyme outside the U.S., we will not know what the reimbursement rates will be until we are ready to market the product and we actually negotiate the rates. If we are unable to obtain sufficiently high reimbursement rates for our products, they may not be commercially viable or our future revenues and gross margins may be adversely affected.

In the future, government price controls or other changes in pricing regulation could restrict the amount that we are able to charge for our current and future products, which would adversely affect our revenue and results of operations.

We expect that, in the future, reimbursement will be increasingly restricted both in the U.S. and internationally. The escalating cost of health care has led to increased pressure on the health care industry to reduce costs. Governmental and private third-party payers have proposed health care reforms and cost reductions. A number of federal and state proposals to control the cost of health care, including the cost of drug treatments, have been made in the U.S. In some foreign markets, the government controls the pricing, which can affect the profitability of drugs. Current government regulations and possible future legislation regarding health care may affect reimbursement for medical treatment by third-party payers, which may render our products not commercially viable or may adversely affect our future revenues and gross margins.

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In the U.S., we expect branded pharmaceutical products to be subject to increasing pricing pressures. Implementation of the Medicare Prescription Drug, Improvement and Modernization Act of 2003 (MMA), providing an out-patient prescription drug benefit under the Medicare program, became effective on January 1, 2006. While it is difficult to predict the final business impact of this legislation, there is additional risk associated with increased pricing pressures. While the MMA prohibits the Secretary of Health and Human Services (HHS) from directly negotiating prescription drug prices with manufacturers, we expect continued challenges to that prohibition over the next several years. Also, the MMA retains the authority of the HHS to prohibit the importation of prescription drugs, but we expect Congress to consider several measures that could remove that authority and allow for importation of products into the U.S. regardless of their safety or cost. If adopted, such legislation would likely have a negative effect on our U.S. sales.

As a result of the passage of the MMA, aged and disabled patients jointly eligible for Medicare and Medicaid will receive certain prescription drug benefits through Medicare, instead of Medicaid, as of January 1, 2006. This may relieve some state budget pressures but is unlikely to result in reduced pricing pressures. Additionally, in the U.S., we are required to provide rebates to state governments on their purchases of certain of our products under state Medicaid programs. Many states have begun to implement supplemental rebates and restricted formularies in their Medicaid programs, and these programs are expected to continue in the post-MMA environment. Other cost containment measures have been adopted or proposed by federal, state, and local government entities that provide or pay for health care. In most international markets, we operate in an environment of government-mandated cost containment programs, which may include price controls, reference pricing, discounts and rebates, restrictions on physician prescription levels, restrictions on reimbursement, compulsory licenses, health economic assessments, and generic substitution. Several states are also attempting to extend discounted Medicaid prices to non-Medicaid patients. Additionally, notwithstanding the federal law prohibiting pharmaceutical importation, several states have implemented importation schemes for their citizens, usually involving a website that links patients to selected Canadian pharmacies. At least one state has such a program for its state employees. In the absence of federal action to curtail state activities, we expect other states to launch importation efforts. As a result, we expect pressures on pharmaceutical pricing to continue.

International operations are also generally subject to extensive price and market regulations, and there are many proposals for additional cost-containment measures, including proposals that would directly or indirectly impose additional price controls or reduce the value of our intellectual property portfolio.

We cannot predict the extent to which our business may be affected by these or other potential future legislative or regulatory developments. However, future price controls or other changes in pricing regulation could restrict the amount that we are able to charge for our current and future products, which would adversely affect our revenue and results of operations.

If we are unable to protect our proprietary technology, we may not be able to compete as effectively.

Where appropriate, we seek patent protection for certain aspects of our technology. Patent protection may not be available for some of the products we are developing. If we must spend significant time and money protecting our patents, designing around patents held by others or licensing, potentially for large fees, patents or other proprietary rights held by others, our business and financial prospects may be harmed.

The patent positions of biopharmaceutical products are complex and uncertain. The scope and extent of patent protection for some of our products and product candidates are particularly uncertain because key information on some of our product candidates has existed in the public domain for many years. Other parties have published the structure of the enzymes and compounds, the methods for purifying or producing the enzymes and compounds or the methods of treatment. The composition and genetic sequences of animal and/or human versions of Aldurazyme, Naglazyme and many of our product candidates, including BH_4, have been published and are believed to be in the public domain. Publication of this information may prevent us from obtaining composition-of-matter patents, which are generally believed to offer the strongest patent protection.

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For enzymes or compounds with no prospect of broad composition-of-matter patents, other forms of patent protection or orphan drug status may provide us with a competitive advantage. As a result of these uncertainties, investors should not rely on patents as a means of protecting our products or product candidates, including Aldurazyme, Naglazyme, Orapred or BH_4.

We own or license patents and patent applications related to Aldurazyme, Naglazyme, Orapred, and certain of our product candidates. However, these patents and patent applications do not ensure the protection of our intellectual property for a number of reasons, including the following:

We do not know whether our patent applications will result in issued patents. For example, we may not have developed a method for treating a disease before others developed similar methods.

Competitors may interfere with our patent process in a variety of ways. Competitors may claim that they invented the claimed invention prior to us. Competitors may also claim that we are infringing on their patents and therefore cannot practice our technology as claimed under our patent. Competitors may also contest our patents by showing the patent examiner that the invention was not original, was not novel or was obvious. In litigation, a competitor could claim that our issued patents are not valid for a number of reasons. If a court agrees, we would lose that patent. As a company, we have no meaningful experience with competitors interfering with our patents or patent applications.