

BIOMARIN PHARMACEUTICAL INC

Form S-3/A

December 05, 2003

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As filed with the Securities and Exchange Commission on December 5, 2003

Registration No. 333-108972

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# SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

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## AMENDMENT NO. 1 TO FORM S-3 REGISTRATION STATEMENT *UNDER* *THE SECURITIES ACT OF 1933*

### **BioMarin Pharmaceutical Inc.**

(Exact name of registrant as specified in its charter)

**Delaware**  
(State or other jurisdiction of incorporation or organization)

**68-0397820**  
(I.R.S. Employer Identification No.)

**371 Bel Marin Keys Boulevard, Suite 210**

**Novato, California 94949**

**(415) 884-6700**

(Address, including zip code, and telephone number,  
including area code, of registrant's principal executive offices)

**Louis Drapeau**

**Vice President, Finance and Chief Financial Officer**

**BioMarin Pharmaceutical Inc.**

**371 Bel Marin Keys Boulevard, Suite 210**

**Novato, California 94949**

**(415) 506-6700**

(Name, address, including zip code, and telephone number, including area code, of agent for service)

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*Copy to:*

**Siobhan McBreen Burke**

**Paul, Hastings, Janofsky & Walker LLP**

**515 South Flower Street, 25th Floor**

**Los Angeles, California 90071-2228**

**(213) 683-6000**

**Approximate date of commencement of proposed sale to the public:** From time to time after the effective date of this Registration Statement.

If the only securities being registered on this form are being offered pursuant to dividend or interest reinvestment plans, please check the following box. "

If any of the securities being registered on this form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, other than securities offered only in connection with dividend or interest reinvestment plans, check the following box. x

If this form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, please check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. "

If this form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. "

If delivery of the prospectus is expected to be made pursuant to Rule 434 under the Securities Act, please check the following box. "

**THE REGISTRANT HEREBY AMENDS THIS REGISTRATION STATEMENT ON SUCH DATE OR DATES AS MAY BE NECESSARY TO DELAY ITS EFFECTIVE DATE UNTIL THE REGISTRANT SHALL FILE A FURTHER AMENDMENT WHICH SPECIFICALLY STATES THAT THIS REGISTRATION STATEMENT SHALL THEREAFTER BECOME EFFECTIVE IN ACCORDANCE WITH SECTION 8(a) OF THE SECURITIES ACT OR UNTIL THE REGISTRATION STATEMENT SHALL BECOME EFFECTIVE ON SUCH DATE AS THE SECURITIES AND EXCHANGE COMMISSION, ACTING PURSUANT TO SAID SECTION 8(a), MAY DETERMINE.**

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The information in this prospectus is not complete and may be changed. The selling securityholders may not sell these securities until the registration statement filed with the Securities and Exchange Commission is effective. This prospectus is not an offer to sell these securities, and is not soliciting an offer to buy these securities, in any state where the offer or sale is not permitted.

**SUBJECT TO COMPLETION DATED DECEMBER 5, 2003**

**PRELIMINARY PROSPECTUS**

**\$125,000,000**

**3.50% Convertible Subordinated Notes Due 2008 and  
the Common Stock Issuable on Conversion of the Notes**

**BioMarin Pharmaceutical Inc.**

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The 3.50% convertible subordinated notes due 2008 are not listed on any securities exchange or included in any automated quotation system. Our common stock currently trades on the Nasdaq National Market and the Swiss SWX New Market under the symbol BMRN. On December 4, 2003, the last reported sale price of our Common Stock on the Nasdaq National Market was \$7.50 per share.

See **Risk Factors** beginning on page 4 to read about risks that you should consider before buying the notes or shares of our common stock.

Neither the Securities and Exchange Commission nor any other regulatory body has approved or disapproved these securities or passed upon the adequacy or accuracy of this prospectus. Any representation to the contrary is a criminal offense.

The date of this prospectus is \_\_\_\_\_, 2003

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**SUMMARY**

*This prospectus contains forward looking statements, which involve risks and uncertainties. Our actual results could differ materially from those anticipated in these forward looking statements as a result of certain factors appearing under Risk Factors and elsewhere in this prospectus.*

*The following summary does not contain all the information that may be important to you. You should read the entire prospectus, including the financial statements and other information incorporated by reference in this prospectus, before making an investment decision.*

We develop enzyme therapies to treat serious, life-threatening diseases and conditions. We leverage our expertise in enzyme biology to develop product candidates for the treatment of genetic diseases, as well as other critical care situations such as cardiovascular surgery. Our first commercial product and our product candidates address markets for which no products are currently available or where current products have been associated with major deficiencies.

Our first product, Aldurazyme® (laronidase), has been approved for marketing in the United States by the United States Food and Drug Administration (FDA), in the European Union by the European Medicines Evaluation Agency (EMA) and other countries for the treatment of mucopolysaccharidosis I (MPS I) disease. MPS I is a debilitating and life-threatening genetic disease caused by the deficiency of (alpha)-L-iduronidase, an enzyme responsible for breaking down certain carbohydrates. MPS I is a progressive disease that afflicts patients from birth and frequently leads to severe disability and early death. As the first drug ever approved for MPS I, Aldurazyme has been granted orphan drug status in the United States and the European Union, which gives Aldurazyme seven years of market exclusivity in the United States and ten years of market exclusivity in the European Union for (alpha)-L-iduronidase for the treatment of MPS I. We have developed Aldurazyme through a joint venture with Genzyme Corporation (Genzyme).

In September 2003, we announced that we halted our Phase 3a study of Neutralase for the reversal of anticoagulation by heparin in primary coronary artery bypass graft (CABG) surgery and that we have terminated the Neutralase program for all indications. Heparin is a carbohydrate drug commonly used as an anticoagulant in a range of surgical procedures such as CABG surgery and angioplasty. Neutralase is a carbohydrate-modifying enzyme that cleaves heparin, allowing coagulation of blood and potentially aiding patient recovery following surgery. The decision to halt the Phase 3a study resulted from a recommendation from an independent Data Safety Monitoring Board (DSMB) and was based on a review of data from enrolled patients, which indicated with high probability that Neutralase would not demonstrate favorable safety and efficacy. Given the expected risk/benefit profile for Neutralase, we decided to stop development of the drug for all indications.

We are developing other enzyme-based therapeutics for the treatment of a variety of diseases and conditions. In October 2003, we completed enrollment in a Phase 3 trial of Aryplase for the treatment of mucopolysaccharidosis VI (MPS VI), another seriously debilitating genetic disease for which no drug treatment currently exists. We have received orphan drug designation for Aryplase for the treatment of MPS VI in the United States and the European Union. We also are developing Vibriplase, a topical enzyme product for use in removing burned skin tissue in preparation for skin grafting or other therapy. A Phase 1 clinical trial of this product in the United Kingdom is expected to be completed in the fourth quarter of 2003. In addition, we are pursuing preclinical development of several other enzyme product candidates for genetic and other diseases. We have retained all worldwide commercial rights to all of our product candidates.

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### **ALDURAZYME**

Our first commercial product, Aldurazyme, has been approved in the United States by the FDA, in the European Union by the EMEA and in other countries for the treatment of MPS I. MPS I is a genetic disease caused by the deficiency of (alpha)-L-iduronidase. Patients with MPS I have multiple debilitating symptoms resulting from the buildup of carbohydrate residues in all tissues in the body. These symptoms include delayed physical and mental growth, enlarged livers and spleens, skeletal and joint deformities, airway obstruction, heart disease, reduced endurance and pulmonary function, and impaired hearing and vision. Most patients with MPS I die from complications associated with the disease as children or teenagers. About 3,400 individuals in developed countries have MPS I, including about 1,000 in the United States and Canada.

Other than Aldurazyme, there are currently no approved drugs for the treatment of MPS I. Bone marrow transplantation has been used to treat severely affected patients, generally under the age of two, with limited success. Bone marrow transplantation is associated with high morbidity and mortality rates as well as with problems inherent in the procedure itself, including graft vs. host disease, graft rejection and donor availability, which severely limit its utility and application.

Aldurazyme is a specific form of recombinant human (alpha)-L-iduronidase that replaces a genetic deficiency of (alpha)-L-iduronidase in MPS I patients, thus reducing or eliminating the build-up of certain carbohydrates in the lysosomes of cells. By eliminating this carbohydrate build-up, Aldurazyme is able to significantly reduce symptoms experienced by these patients, including improved pulmonary function, improved endurance, decreased joint stiffness, decreased fatigue, improved vision, reduced airway obstruction, weight and height gain, improved cardiac function and the elimination of severe headaches.

In 1998, we formed a 50/50 joint venture with Genzyme for the worldwide development and commercialization of Aldurazyme. We are responsible for product development, manufacturing and United States regulatory submissions. Genzyme is responsible for sales, marketing, distribution, obtaining reimbursement for Aldurazyme worldwide and international regulatory submissions.

The FDA has granted Aldurazyme orphan drug designation, which provides our joint venture with exclusive rights to market Aldurazyme in the United States for seven years from the date of FDA approval. In addition, the EMEA has granted Aldurazyme orphan drug designation, giving ten years of market exclusivity in the European Union. However, different drugs can be approved for the same condition.

### **ARYPLASE**

We are developing Aryplase as an enzyme replacement therapy for the treatment of MPS VI, a debilitating genetic disease similar to MPS I. Aryplase is a specific form of recombinant human *N*-acetylgalactosamine 4-sulfatase (also known as arylsulfatase B). Aryplase has received fast track designation from the FDA as well as orphan drug designation for the treatment of MPS VI in the United States and in the European Union. In March 2002, we initiated an open-label, multi-national Phase 2 clinical trial to evaluate the efficacy, safety and pharmacokinetics of weekly intravenous infusions of 1.0 mg/kg of Aryplase in ten MPS VI patients. The trial was completed in January 2003 and results demonstrated that Aryplase is well tolerated and is associated with improvements in several clinical end points. Among other positive results, on average, subjects demonstrated a 62% and 98% improvement in distance walked at 6 minutes and 12 minutes, respectively, during a 12-minute walk test. Additionally, on average, subjects demonstrated an improvement of 109% over base line in the number of stairs climbed during a 3-minute test. We began enrolling patients in an international double blind, placebo controlled Phase 3 clinical trial of Aryplase in July of 2003. We expect to complete the Phase 3 trial in the first quarter of 2004.





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### **OTHER PRODUCT DEVELOPMENT PROGRAMS**

#### **Vibrilase**

We are developing Vibrilase for use in removing burned skin in preparation for skin grafting or other therapy. In the second quarter of 2002, we initiated a Phase 1 clinical trial of this product candidate in the United Kingdom. In March 2003, we announced that we completed the Phase 1a portion of the trial and we expect to complete the entire Phase 1 trial in 2003.

#### **Phenoptin and Phenylase**

We are developing Phenoptin and Phenylase as potential treatments for patients with phenylketonuria (PKU), a genetic disease in which the body cannot properly metabolize the amino acid phenylalanine. If left untreated, elevated levels of phenylalanine lead to brain damage and severe mental retardation.

In November 2003, we announced plans to begin clinical development with Phenoptin, an enzyme cofactor that is a second generation, proprietary oral form of tetrahydrobiopterin, for the treatment of PKU. We are evaluating Phenoptin for the treatment of mild to moderate forms of PKU, which represents approximately half of the PKU cases. We have entered into an agreement with Merck Eprova AG, a subsidiary of Merck KGaA, for the development, manufacturing and supply of Phenoptin.

We are evaluating Phenylase, phenylalanine ammonia lyase (PAL), as an injectable enzyme replacement therapy for the more severe forms of PKU. Phenylase is currently in preclinical development.

Compliance with existing treatment of PKU, consisting of highly restricted and generally unpalatable diets, usually only occurs through middle childhood to ensure normal brain development. Recent data demonstrates that adolescent and adult PKU sufferers who no longer follow restricted diets suffer from a number of psychological and neurological symptoms. Phenoptin and Phenylase are intended to enable disease control without the need for restrictive diets.

#### **NeuroTrans**

NeuroTrans is a novel technology that is designed to allow large molecules such as proteins to be transported efficiently across the blood-brain barrier after administration by traditional intravenous delivery. We are exploring the delivery of lysosomal enzymes to the brain and will be seeking partners on the delivery of other therapeutics such as neurotrophic factors and cancer drugs.

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Our principal executive offices are located at 371 Bel Marin Keys Boulevard, Suite 210, Novato, CA 94949 and our telephone number is (415) 506-6700. Our website is [www.BMRN.com](http://www.BMRN.com). Information on our website is not incorporated by reference in this prospectus.

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**RISK FACTORS**

*An investment in our securities involves a high degree of risk. We operate in a dynamic and rapidly changing industry that involves numerous risks and uncertainties. Before purchasing our securities, you should carefully consider the following risk factors, as well as other information contained in this prospectus or incorporated by reference into this prospectus, in evaluating an investment in the securities offered by this 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 trading price of our securities 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 only recently approved for commercial sale in the United States and the European Union and has only generated nominal sales revenue to date. We have no sales revenues from our product candidates. As of September 30, 2003, we had an accumulated deficit of approximately \$275.7 million. We expect to continue to operate at a net loss for the foreseeable future. Our future profitability depends on the successful commercialization of Aldurazyme by our joint venture partner, Genzyme, our receiving 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.

**If we fail to obtain the capital necessary to fund our operations, we will be unable to complete our product development programs.**

In the future, we may need to raise substantial additional capital to fund operations. 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.

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 commercialize Aldurazyme;

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

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the time and cost necessary to obtain regulatory approvals;

the time and cost necessary to develop commercial manufacturing processes, including quality systems, and to build or acquire manufacturing capabilities;

the time and cost necessary to respond to technological and market developments; and

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.

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Moreover, our fixed expenses such as rent, license payments and other contractual commitments are substantial and will increase in the future. These fixed expenses will increase due to the payment of interest on our convertible debt and because we may enter into:

additional leases for new facilities and capital equipment;

additional licenses and collaborative agreements;

additional contracts for consulting, maintenance and administrative services;

additional contracts for product manufacturing; and

additional asset-based financing facilities.

We believe that our cash, cash equivalents and short-term investment securities balances at September 30, 2003, will be sufficient to meet our operating and capital requirements through at least the end of 2005. These estimates are based on assumptions and estimates, which may prove to be wrong. As a result, we may need or choose to obtain additional financing during that time.

**If we fail to obtain or maintain regulatory approval to commercially manufacture or sell our future drug products, 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 United States and in foreign jurisdictions. In the United States, 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. Only one of our drug products has received regulatory approval to be commercially marketed and sold in the United States and the European Union. If we fail to obtain regulatory approval for our other drugs, we will be unable to market and sell those drug products. Because of the risks and uncertainties in biopharmaceutical development, our drug products could take a significantly longer time to gain regulatory approval than we expect or may never gain approval. 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, reporting adverse reactions and other information, and product recall. 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. 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 clinical trials will be 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 drug product. We expect the number of preclinical studies and clinical trials that the regulatory authorities will require

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will vary depending on the drug product, 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 drug products. 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 on the target human patients in order to receive regulatory approval for commercial sale.

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Adverse or inconclusive clinical results would stop us from filing for regulatory approval of our drug products. 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.

Typically, if a drug product is intended to treat a chronic disease, as is the case with some of the product candidates we are developing, 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 independent Data Safety Monitoring Board for the Neutralase Phase 3a clinical study recommended termination of the Phase 3a study as it determined that the advantages of Neutralase would be unlikely to outweigh its side effects. The study data included two patient deaths. One patient that died was found to have used protamine and not Neutralase. The other patient that died used Neutralase; however, it is our belief, based on the data that has been unblinded to date, that the cause of death was not likely related to Neutralase. Based upon the expected risk/benefit profile of Neutralase, we terminated the Neutralase development program for all indications.

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

Aryplase has obtained fast track designation, which provides certain advantageous procedures and guidelines with respect to the review by the FDA of the Common Technical Document (CTD) for this product and which may result in our receipt of an initial response from the FDA earlier than would be received if this product had not received a fast track designation. However, these procedures and guidelines do not guarantee 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 the review process or approval for Aryplase is delayed, realizing revenue from the sale of Aryplase will be delayed and the capital necessary to fund this program will be increased.

**We will not be able to sell our products if we fail to comply with manufacturing regulations.**

Before we can begin commercial manufacture of our products, we must obtain regulatory approval of our manufacturing facilities and processes. In addition, manufacture of our drug products must comply with the FDA's current Good Manufacturing Practices regulations, commonly known as cGMP. The cGMP regulations govern facility compliance, quality control and documentation policies and procedures. 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 Galli Drive and our Bel Marin Keys Boulevard manufacturing facilities have been inspected and licensed by the State of California for clinical pharmaceutical manufacture and our Galli Drive facility has been approved by the FDA and the EMEA for the commercial manufacture of Aldurazyme.

Due to the complexity of the processes used to manufacture our products, we may be unable to pass federal or international regulatory inspections in a cost effective manner. For the same reason, any potential third party



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manufacturer of our drug products may be unable to comply with cGMP regulations in a cost effective manner. If we are unable to comply with manufacturing regulations, we will not be able to sell our products.

**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 European Community 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 United States. 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 European Community with a ten-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 eligible drugs, we plan to rely on the exclusivity period under the orphan drug designation 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.

Even though we have obtained orphan drug designation for certain of our product candidates and even if we obtain orphan drug designation for other products we develop, 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. 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.**

Two of our lead product programs, Aldurazyme and Aryplase, 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 Aryplase targets patients with MPS VI. We estimate that there are approximately 3,400 patients with MPS I and 1,100 patients with MPS VI in the developed world. We believe that we will need to market worldwide to achieve significant market share. In addition, we are developing other drug candidates to treat conditions, such as other genetic diseases and serious burn wounds, with small patient populations. Due to the expected costs of treatment for Aldurazyme and Aryplase, we may be unable to obtain sufficient market share for our drug products at a price high enough to justify our product development efforts.

**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.**

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The course of treatment for patients with MPS I using Aldurazyme and for patients with MPS VI using Aryplase is expected to be 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 Aryplase 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.

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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 no expertise obtaining reimbursement. We are relying on the expertise of our joint venture partner Genzyme to obtain reimbursement for the costs of Aldurazyme. In addition, we will need to develop our own reimbursement expertise for future drug candidates unless we enter into collaborations with other companies with the necessary expertise. For our future products, 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, our products may not be commercially viable or our future revenues and gross margins may be adversely affected.

We expect that, in the future, reimbursement will be increasingly restricted both in the United States 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 United States. In some foreign markets, the government controls the pricing, which would 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.

### **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, for large fees, patents or other proprietary rights held by others, our business and financial prospects may be harmed.

The patent positions of biotechnology products are complex and uncertain. The scope and extent of patent protection for some of our products are particularly uncertain because key information on some of the products we are developing 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 and many of our product candidates have been published and are believed to be in the public domain. The composition and genetic sequences of other MPS enzymes that we intend to develop as products have also been published. Publication of this information may prevent us from obtaining composition-of-matter patents, which are generally believed to offer the strongest patent protection.

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.

We own or license patents and patent applications related to Aldurazyme 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 other reasons, including the following:

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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

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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.

Enforcing patents is expensive and may absorb significant time of our management. Management would spend less time and resources on developing products, which could increase our research and development expenses and delay product programs.

Receipt of a patent may not provide much practical protection. If we receive a patent with a narrow scope, then it will be easier for competitors to design products that do not infringe on our patent.

In addition, competitors also seek patent protection for their technology. Due to the number of patents in our field of technology, we cannot be certain that we do not infringe on those patents or that we will not infringe on patents granted in the future. If a patent holder believes our product infringes on their patent, the patent holder may sue us even if we have received patent protection for our technology. If someone else claims we infringe on their technology, we would face a number of issues, including the following:

Defending a lawsuit takes significant time and can be very expensive.

If the court decides that our product infringes on the competitor's patent, we may have to pay substantial damages for past infringement.

The court may prohibit us from selling or licensing the product unless the patent holder licenses the patent to us. The patent holder is not required to grant us a license. If a license is available, we may have to pay substantial royalties or grant cross licenses to our patents.

Redesigning our product so it does not infringe may not be possible or could require substantial funds and time.

It is also unclear whether our trade secrets are adequately protected. While we use reasonable efforts to protect our trade secrets, our employees or consultants may unintentionally or willfully disclose our information to competitors. Enforcing a claim that someone else illegally obtained and is using our trade secrets, like patent litigation, is expensive and time consuming, and the outcome is unpredictable. In addition, courts outside the United States are sometimes less willing to protect trade secrets. Our competitors may independently develop equivalent knowledge, methods and know-how.

We may also support and collaborate in research conducted by government organizations or by universities. These government organizations and universities may be unwilling to grant us any exclusive rights to technology or products derived from these collaborations prior to entering into the relationship.

If we do not obtain required licenses or rights, we could encounter delays in product development while we attempt to design around other patents or even be prohibited from developing, manufacturing or selling products requiring these licenses. There is also a risk that disputes may arise as to the rights to technology or products developed in collaboration with other parties.

**The United States Patent and Trademark Office has issued three patents to a third party that relate to (alpha)-L-iduronidase. If we are not able to successfully challenge these patents, we may be prevented from producing Aldurazyme in the United States unless and until we obtain a license.**

The United States Patent and Trademark Office has issued three patents to a third party that include composition-of-matter, isolated genomic nucleotide sequences, vectors including the sequences, host cells containing the vectors, and method of use claims for human recombinant (alpha)-L-iduronidase. Our lead drug product, Aldurazyme, is based on human recombinant (alpha)-L-iduronidase. We believe that these patents are

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invalid or not infringed on a number of grounds. A corresponding patent application was filed in the European Patent Office claiming composition-of-matter for human recombinant (alpha)-L-iduronidase, and it was rejected over prior art and withdrawn and cannot be re-filed. However, corresponding applications are still pending in Canada and Japan, and these applications are being prosecuted by the applicants. We do not know whether any of these applications will issue as patents or the scope of the claims that would issue from these applications. In addition, under United States law, issued patents are entitled to a presumption of validity, and our challenges to the United States patents may be unsuccessful. Even if we are successful, challenging the United States patents may be expensive, require our management to devote significant time to this effort and may adversely impact commercialization of Aldurazyme in the United States.

The holder of the patents described above has granted an exclusive license for products relating to these patents to one of our competitors. If we are unable to successfully challenge the patents, we may be unable to produce Aldurazyme in the United States (or in Canada or Japan, should patents issue in these countries) unless we can obtain a sublicense from the current licensee. The current licensee is not required to grant us a license and even if a license is available, we may have to pay substantial license fees, which could adversely affect our business and operating results.

**If our joint venture with Genzyme were terminated, we could be barred from commercializing Aldurazyme or our ability to successfully commercialize Aldurazyme would be delayed or diminished.**

We are relying on Genzyme to apply the expertise it has developed through the launch and sale of other enzyme-based products to the marketing of Aldurazyme. We have no experience selling, marketing or obtaining reimbursement for pharmaceutical products. In addition, without Genzyme we would be required to pursue foreign regulatory approvals. We have no experience in seeking foreign regulatory approvals.

Either Genzyme or we may terminate the joint venture for specified reasons, including if the other party is in material breach of the agreement or has experienced a change of control or has declared bankruptcy and also is in breach of the agreement. Although we are not currently in breach of the joint venture agreement and we believe that Genzyme is not currently in breach of the joint venture agreement, there is a risk that either party could breach the agreement in the future. Either party may also terminate the agreement upon one-year prior written notice for any reason.

If the joint venture is terminated for breach, the non-breaching party would be granted, exclusively, all of the rights to Aldurazyme and any related intellectual property and regulatory approvals and would be obligated to buy out the breaching party's interest in the joint venture. If we are the breaching party, we would lose our rights to Aldurazyme and the related intellectual property and regulatory approvals. If the joint venture is terminated without cause, the non-terminating party would have the option, exercisable for one year, to buy out the terminating party's interest in the joint venture and obtain all rights to Aldurazyme exclusively. In the event of termination of the buy out option without exercise by the non-terminating party as described above, all right and title to Aldurazyme is to be sold to the highest bidder, with the proceeds to be split equally between Genzyme and us.

If the joint venture is terminated by either party because the other declared bankruptcy and is also in breach of the agreement, the terminating party would be obligated to buy out the other and would obtain all rights to Aldurazyme exclusively. If the joint venture is terminated by a party because the other party experienced a change of control, the terminating party shall notify the other party, the offeree, of its intent to buy out the offeree's interest in the joint venture for a stated amount set by the terminating party at its discretion. The offeree must then either accept this offer or agree to buy the terminating party's interest in the joint venture on those same terms. The party who buys out the other would then have exclusive rights to Aldurazyme.

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If we were obligated, or given the option, to buy out Genzyme's interest in the joint venture, and gain exclusive rights to Aldurazyme, we may not have sufficient funds to do so and we may not be able to obtain the



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financing to do so. If we fail to buy out Genzyme's interest we may be held in breach of the agreement and may lose any claim to the rights to Aldurazyme and the related intellectual property and regulatory approvals. We would then effectively be prohibited from developing and commercializing the product.

Termination of the joint venture in which we retain the rights to Aldurazyme could cause us significant difficulties in obtaining third-party reimbursement and delays or failure to obtain foreign regulatory approval, any of which could hurt our business and results of operations. Since Genzyme funds 50% of the joint venture's product inventory and operating expenses, the termination of the joint venture would double our financial burden and reduce the funds available to us for other product programs.

**If we are unable to successfully develop manufacturing processes for our drug products to produce sufficient quantities and at acceptable cost, we may be unable to meet demand for our products and lose potential revenue, have reduced margins or be forced to terminate a program.**

Although we have successfully manufactured Aldurazyme at commercial scale and within our cost parameters, due to the complexity of manufacturing our products we may not be able to manufacture any other drug product successfully with a commercially viable process or at a scale large enough to support their respective commercial markets or at acceptable margins.

Our manufacturing processes may not meet initial expectations and we may encounter problems with any of the following if we attempt to increase the scale or size or improve the commercial viability of our manufacturing processes:

design, construction and qualification of manufacturing facilities that meet regulatory requirements;

schedule;

reproducibility;

production yields;

purity;

costs;

quality control and assurance systems;

shortages of qualified personnel; and

compliance with regulatory requirements.

Improvements in manufacturing processes typically are very difficult to achieve and are often very expensive and may require extended periods of time to develop. If we contract for manufacturing services with an unproven process, our contractor is subject to the same uncertainties, high standards and regulatory controls.

The availability of suitable contract manufacturing at scheduled or optimum times is not certain. The cost of contract manufacturing is greater than internal manufacturing and therefore our manufacturing processes must be of higher productivity to result in equivalent margins.

We have built-out approximately 54,000 square feet at our Novato facilities for manufacturing capability for Aldurazyme including related quality control laboratories, materials capabilities, and support areas. We expect to add additional capabilities in stages over time, which could create additional operational complexity and challenges. We expect that the manufacturing process of all of our new drug products, including Aryplase, will require significant time and resources before we can begin to manufacture them (or have them manufactured by third parties) in commercial quantity at an acceptable cost.

In order to achieve our product cost targets, we must develop efficient manufacturing processes either by:

improving the product yield from our current cell lines, which are colonies of cells that have a common genetic makeup;

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improving the manufacturing processes licensed from others; or

developing more efficient, lower cost recombinant cell lines and production processes.

A recombinant cell line is a cell line with foreign DNA inserted that is used to produce an enzyme or other protein that it would not have otherwise produced. The development of a stable, high production cell line for any given enzyme is difficult, expensive and unpredictable and may not result in adequate yields. In addition, the development of protein purification processes is difficult and may not produce the high purity required with acceptable yield and costs or may not result in adequate shelf-lives of the final products. If we are not able to develop efficient manufacturing processes, the investment in manufacturing capacity sufficient to satisfy market demand will be much greater and will place heavy financial demands upon us. If we do not achieve our manufacturing cost targets we may be unable to meet demand for our products and lose potential revenue, have reduced margins or be forced to terminate a program.

In addition, our manufacturing processes subject us to a variety of federal, state and local laws and regulations governing the use, generation, manufacture, storage, handling and disposal of hazardous materials and wastes resulting from their use. We may incur significant costs in complying with these laws and regulations.

**If our manufacturing processes have a higher than expected failure rate, we may be unable to meet demand for our products and lose potential revenue, have reduced margins, or be forced to terminate a program.**

The processes we use to manufacture our product and product candidates are extremely complex. Many of the processes include biological systems, which add significant additional complexity, as compared to chemical systems. We expect that, from time to time, consistent with biotechnology industry expectations, certain production lots will fail to produce pharmaceutical grade product. To date, our historical failure rates for all of our product programs, including Aldurazyme, have been within our expectations, which are based on industry norms.

In order to produce product within our time and cost parameters, we must continue to produce product within expected failure parameters. Because of the complexity of our manufacturing processes, it may be difficult or impossible for us to determine the cause of any particular lot failure; and we must effectively and timely take corrective action in response to any failure.

If we are unable to effectively address any product manufacturing issues, we may be unable to meet demand for our products and lose potential revenue, have reduced margins, or be forced to terminate a program.

**Our sole manufacturing facility for Aldurazyme is located near known earthquake fault zones, and the occurrence of an earthquake or other catastrophic disaster could cause damage to our facility and equipment, which could materially impair our ability to manufacture Aldurazyme.**

Our Novato, California facility is our only manufacturing facility for Aldurazyme. It is located in the San Francisco Bay area near known earthquake fault zones and is vulnerable to significant damage from earthquakes. We are also vulnerable to damage from other types of disasters, including fires, floods, power loss and similar events. If any disaster were to occur, our ability to manufacture Aldurazyme could be seriously, or potentially completely, impaired, we could incur delays in our commercialization efforts and our revenue from the sale of Aldurazyme could be seriously impaired. The insurance we maintain may not be adequate to cover our losses resulting from disasters or other business interruptions.

**If we are unable to create marketing and distribution capabilities or to enter into agreements with third parties to do so, our ability to generate revenues will be diminished.**

If we cannot expand our marketing and distribution capabilities either by developing our own sales and marketing organization or by entering into agreements with others, we may be unable to successfully sell our

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products. We believe that developing an internal sales and distribution capability will be expensive and time consuming. Alternatively, we may enter into agreements with third parties to market our products. For example, under our joint venture with Genzyme, Genzyme is responsible for marketing and distributing Aldurazyme. However, these third parties may not be capable of successfully selling any of our drug products.

We may compete with other pharmaceutical companies with experienced and well-funded sales and marketing operations targeting these specific physician and institutional audiences. We may not be able to develop our own sales and marketing force at all, or of a size that would allow us to compete with these other companies. If we elect to enter into third-party marketing and distribution agreements in order to sell into these markets, we may not be able to enter into these agreements on acceptable terms, if at all. If we cannot compete effectively in these specific physician and institutional markets, it would adversely affect sales of our product candidates.

**If we fail to compete successfully with respect to product sales, we may be unable to generate sufficient sales to recover our expenses related to the development of a product program or to justify continued marketing of a product.**

Our competitors may develop, manufacture and market products that are more effective or less expensive than ours. They may also obtain regulatory approvals for their products faster than we can obtain them (including those products with orphan drug designation) or commercialize their products before we do. With respect to Aryplase, if our competitors successfully commercialize a product that treats MPS VI before we do, we may effectively be precluded from developing a product to treat that disease because the patient population of the disease is so small. If one of our competitors gets orphan drug exclusivity, we could be precluded from marketing our version for seven years in the United States and ten years in the European Union. However, different drugs can be approved for the same condition. If we do not compete successfully, we may be unable to generate sufficient sales to recover our expenses related to the development of a product program or to justify continued marketing of a product.

**If we fail to compete successfully with respect to acquisitions, joint venture and other collaboration opportunities, we may be limited in our ability to develop new products and to continue to expand our product pipeline.**

Our competitors compete with us to attract organizations for acquisitions, joint ventures, licensing arrangements or other collaborations. To date, several of our product programs have been acquired through acquisitions, such as NeuroTrans, and several of our product programs have been developed through licensing or collaborative arrangements, such as Aldurazyme, Aryplase and Vibrilase. These collaborations include licensing proprietary technology from, and other relationships with, academic research institutions. If our competitors successfully enter into partnering arrangements or license agreements with academic research institutions, we will then be precluded from pursuing those specific opportunities. Since each of these opportunities is unique, we may not be able to find a substitute. Several pharmaceutical and biotechnology companies have already established themselves in the field of enzyme therapeutics, including Genzyme, our joint venture partner. These companies have already begun many drug development programs, some of which may target diseases that we are also targeting, and have already entered into partnering and licensing arrangements with academic research institutions, reducing the pool of available opportunities.

Universities and public and private research institutions also compete with us. While these organizations primarily have educational or basic research objectives, they may develop proprietary technology and acquire patents that we may need for the development of our drug products. We will attempt to license this proprietary technology, if available. These licenses may not be available to us on acceptable terms, if at all. If we are unable to compete successfully with respect to acquisitions, joint venture and other collaboration opportunities, we may be limited in our ability to develop new products and to continue to expand our product pipeline.

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**If we do not achieve our projected development goals in the time frames we announce and expect, the commercialization of our products may be delayed and the credibility of our management may be adversely affected and, as a result, our stock price may decline.**

For planning purposes, we estimate the timing of the accomplishment of various scientific, clinical, regulatory and other product development goals, which we sometimes refer to as milestones. These milestones may include the commencement or completion of scientific studies and clinical trials and the submission of regulatory filings. From time to time, we publicly announce the expected timing of some of these milestones. All of these milestones are based on a variety of assumptions. The actual timing of these milestones can vary dramatically compared to our estimates, in many cases for reasons beyond our control. If we do not meet these milestones as publicly announced, the commercialization of our products may be delayed and the credibility of our management may be adversely affected and, as a result, our stock price may decline.

**If we fail to manage our growth or fail to recruit and retain personnel, our product development programs may be delayed.**

Our rapid growth has strained our managerial, operational, financial and other resources. We expect this growth to continue. Based on the recent approval of Aldurazyme by the FDA and European Union, and other countries, we expect that our joint venture with Genzyme will be required to devote additional resources in the immediate future to support the commercialization of Aldurazyme.

To manage expansion effectively, we need to continue to develop and improve our research and development capabilities, manufacturing and quality capacities, sales and marketing capabilities and financial and administrative systems. Our staff, financial resources, systems, procedures or controls may be inadequate to support our operations and our management may be unable to manage successfully future market opportunities or our relationships with customers and other third parties.

Our future growth and success depend on our ability to recruit, retain, manage and motivate our employees. The loss of key scientific, technical and managerial personnel may delay or otherwise harm our product development programs. Any harm to our research and development programs would harm our business and prospects.

Because of the specialized scientific and managerial nature of our business, we rely heavily on our ability to attract and retain qualified scientific, technical and managerial personnel. In particular, the loss of Fredric D. Price, our Chairman and Chief Executive Officer, or Emil D. Kakkis, M.D., Ph.D., our Senior Vice President of Business Operations or Christopher M. Starr, Ph.D., our Senior Vice President of Scientific Operations, could be detrimental to us if we cannot recruit suitable replacements in a timely manner. While Mr. Price, Dr. Kakkis and Dr. Starr are parties to employment agreements with us, these agreements do not guarantee that they will remain employed with us in the future. In addition, these agreements do not restrict their ability to compete with us after their employment is terminated. The competition for qualified personnel in the biopharmaceutical field is intense. Due to this intense competition, we may be unable to continue to attract and retain qualified personnel necessary for the development of our business.

**Changes in methods of treatment of disease could reduce demand for our products.**

Even if our drug products are approved, doctors must use treatments that require using those products. If doctors elect a different course of treatment from that which includes our drug products, this decision would reduce demand for our drug products. For example if in the future gene therapy becomes widely used as a treatment of genetic diseases, the use of enzyme replacement therapy, like Aldurazyme, in MPS diseases could be greatly reduced. Changes in treatment method can be caused by the introduction of other companies' products or the development of

new technologies or surgical procedures which may not directly compete with ours, but which have the effect of changing how doctors decide to treat a disease.

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### **If product liability lawsuits are successfully brought against us, we may incur substantial liabilities.**

We are exposed to the potential product liability risks inherent in the testing, manufacturing and marketing of human pharmaceuticals. The BioMarin/Genzyme LLC maintains clinical liability insurance for Aldurazyme with aggregate loss limits of \$5.0 million and has obtained additional coverage in connection with the commercialization of Aldurazyme. We have obtained insurance against product liability lawsuits with aggregate loss limits of \$15.0 million. Pharmaceutical companies must balance the cost of insurance with the level of coverage based on estimates of potential liability. Historically, the potential liability associated with product liability lawsuits for pharmaceutical products has been unpredictable. Although we believe that our current insurance is a reasonable estimate of our potential liability and represents a commercially reasonable balancing of the level of coverage as compared to the cost of the insurance, we may be subject to claims in connection with our current clinical trials for Aldurazyme, Aryplase and Vibrilase or in connection with the clinical trials for our now terminated program for Neutralase for which our insurance coverage is not adequate.

The product liability insurance we will need to obtain in connection with the commercial sales of our product candidates if and when they receive regulatory approval may be unavailable in meaningful amounts or at a reasonable cost. In addition, while we take, and continue to take what we believe are appropriate precautions, we may be unable to avoid significant liability if any product liability lawsuit is brought against us. If we are the subject of a successful product liability claim that exceeds the limits of any insurance coverage we obtain, we may incur substantial liabilities that would adversely affect our earnings and require the commitment of capital resources that might otherwise be available for the development and commercialization of our product programs.

## **RISKS RELATED TO THE SECURITIES OFFERED BY THIS PROSPECTUS**

### **Anti-takeover provisions in our charter documents, our stockholders' rights plan and under Delaware law may make an acquisition of us, which may be beneficial to our stockholders, more difficult.**

We are incorporated in Delaware. Certain anti-takeover provisions of Delaware law and our charter documents as currently in effect may make a change in control of our company more difficult, even if a change in control would be beneficial to the stockholders. Our anti-takeover provisions include provisions in the certificate of incorporation providing that stockholders' meetings may only be called by the board of directors and a provision in the bylaws providing that the stockholders may not take action by written consent. Additionally, our board of directors has the authority to issue an additional 249,886 shares of preferred stock and to determine the terms of those shares of stock without any further action by the stockholders. The rights of holders of our common stock are subject to the rights of the holders of any preferred stock that may be issued. The issuance of preferred stock could make it more difficult for a third party to acquire a majority of our outstanding voting stock. Delaware law also prohibits corporations from engaging in a business combination with any holders of 15% or more of their capital stock until the holder has held the stock for three years unless, among other possibilities, the board of directors approves the transaction. Our board of directors may use these provisions to prevent changes in the management and control of our company. Also, under applicable Delaware law, our board of directors may adopt additional anti-takeover measures in the future.

In September 2002, our board of directors authorized a stockholder rights plan and related dividend of one preferred share purchase right for each share of our common stock outstanding at that time. In connection with an increase in our authorized common stock, our board approved an amendment to this plan in June 2003. As long as these rights are attached to our common stock, we will issue one right with each new share of common stock so that all shares of our common stock will have attached rights. When exercisable, each right will entitle the registered holder to purchase from us one two-hundredth of a share of our Series B Junior Participating Preferred Stock at a price of \$35.00 per  $\frac{1}{200}$  of a Preferred Share, subject to adjustment.



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The rights are designed to assure that all of our stockholders receive fair and equal treatment in the event of any proposed takeover of us and to guard against partial tender offers, open market accumulations and other abusive tactics to gain control of us without paying all stockholders a control premium. The rights will cause

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substantial dilution to a person or group that acquires 15% or more of our stock on terms not approved by our board of directors. However, the rights may have the effect of making an acquisition of us, which may be beneficial to our stockholders, more difficult, and the existence of such rights may prevent or reduce the likelihood of a third party making an offer for an acquisition of us.

**Our stock price may be volatile, and an investment in our stock could suffer a decline in value.**

Our valuation and stock price since the beginning of trading after our initial public offering have had no meaningful relationship to current or historical earnings, asset values, book value or many other criteria based on conventional measures of stock value. The market price of our common stock will fluctuate due to factors including:

product sales and profitability of Aldurazyme;

progress of Aryplase and our other lead drug products through the regulatory process;

results of clinical trials, announcements of technological innovations or new products by us or our competitors;

government regulatory action affecting our drug products or our competitors' drug products in both the United States and foreign countries;

developments or disputes concerning patent or proprietary rights;

general market conditions and fluctuations for the emerging growth and biopharmaceutical market sectors; economic conditions in the United States or abroad;

actual or anticipated fluctuations in our operating results;

broad market fluctuations in the United States or in Europe, which may cause the market price of our common stock to fluctuate; and

changes in company assessments or financial estimates by securities analysts.

In addition, the value of our common stock may fluctuate because it is listed on both the Nasdaq National Market and the Swiss Exchange's SWX New Market. Listing on both exchanges may increase stock price volatility due to:

trading in different time zones;

different ability to buy or sell our stock;

different market conditions in different capital markets; and

different trading volume.

In the past, following periods of large price declines in the public market price of a company's securities, securities class action litigation has often been initiated against that company. Litigation of this type could result in substantial costs and diversion of management's attention and resources, which would hurt our business. Any adverse determination in litigation could also subject us to significant liabilities.

**You should consider the United States federal income tax consequences of owning the notes and the shares of common stock issuable upon conversion of the notes.**

We intend to treat the notes as contingent payment debt instruments for United States federal income tax purposes. As a result of such treatment, an United States investor who is a holder of notes, you will be required to include amounts in income, as ordinary income, in advance of the receipt of the cash or other property attributable thereto. The amount of interest income required to be included by an United States noteholder for each year may be in excess of the fixed interest (and contingent interest, if any) that accrues on the notes. An

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United States noteholder will recognize gain or loss on the sale, exchange, conversion or redemption of a note in an amount equal to the difference between the amount realized on the sale, exchange, conversion or redemption, including the fair market value of any of our common stock received upon conversion, and the noteholder's adjusted tax basis in the note. Any gain recognized by an United States noteholder on the sale, exchange, conversion or redemption of a note generally will be capital gain; any loss will be ordinary loss to the extent of the interest previously included in income, and thereafter, capital loss. Non-United States noteholders are urged to consult their tax advisors regarding a prospective purchase of the notes. For more information, see Certain United States Federal Income Tax Considerations.

**Unless we are able to generate sufficient cash flow from operations, we may not be able to make the required interest and principal payments due under the notes.**

To date, we have not generated positive cash flow from operations. If we are not able to generate sufficient cash flow, we will only be able to pay the interest and principal due under the notes from available cash or from subsequent financing activities. We may not have sufficient available cash and we may be unable to refinance the notes at all or on terms as favorable as the terms of the notes.

**We may not have the ability to raise the funds necessary to finance any repurchase offer required by the indenture.**

If a repurchase event (as defined in the indenture) occurs, each holder of the notes may require us to repurchase all or a portion of the holder's notes. We cannot assure you that there will be sufficient funds available for any required repurchases of these securities if a repurchase event occurs. In addition, the terms of any agreements related to borrowing which we may enter from time to time may prohibit or limit or make our repurchase of notes an event of default under those agreements. If we fail to repurchase the notes in that circumstance, we will be in default under the indenture governing the notes. See Description of Notes Holders May Require Us to Repurchase Their Notes Upon a Repurchase Event.

**No public market exists for the notes. The failure of a market to develop could affect your ability to, and the price at which you may, resell your notes.**

The notes were issued in June 2003, and there is currently no active trading market. We do not intend to list the notes on any national securities exchange or automated quotation system. Accordingly, we cannot predict whether an active trading market for the notes will develop or be sustained. If an active trading market for the notes fails to develop or be sustained, holders of the notes may experience difficulty in reselling, or an inability to sell, the notes and the trading price for the notes could fall.

Moreover, even if an active trading market for the notes were to develop, the notes could trade at prices that may be lower than the initial offering price of the notes. Future trading prices of the notes will depend on many factors, including, among other things, prevailing interest rate, our operating results, the price of our common stock and the market for similar securities. Historically, the market for convertible debt has been subject to disruptions that have caused volatility in prices. It is possible that the market for the notes will be subject to disruptions which may have a negative effect on the holders of the notes, regardless of our prospects or financial performance.

**The notes will be subordinated to our senior indebtedness and will be effectively subordinated to all liabilities of our subsidiaries.**

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The notes are junior in right of payment to all of our existing and future senior indebtedness, and are effectively subordinated to all liabilities of our subsidiaries, including trade payables. As of September 30, 2003, we and our subsidiaries had approximately \$4.1 million of consolidated indebtedness effectively ranking senior to the notes. The indenture governing the notes does not restrict the incurrence of senior indebtedness or other

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debt by us or our subsidiaries. All of our commercial operations related to Aldurazyme are conducted through our joint venture with Genzyme. None of our subsidiaries has guaranteed or otherwise become obligated with respect to the notes and, as a result, the notes will be effectively subordinated to all indebtedness and other obligations of our subsidiaries with respect to our subsidiaries' assets. By reason of such subordination, in the event of the insolvency, bankruptcy, liquidation, reorganization, dissolution or winding up of our business, our assets will be available to pay the amounts due on the notes only after all of our senior indebtedness has been paid in full, and, therefore, there may not be sufficient assets remaining to pay amounts due on any or all of the notes then outstanding. See "Description of Notes" Subordination of Notes.

**We have made only limited covenants in the indenture, which may not protect a noteholder's investment if we experience significant adverse changes in our financial condition or results of operations.**

The indenture governing the notes does not:

require us to maintain any financial ratios or specified levels of net worth, revenues, income, cash flow or liquidity, and therefore, does not protect holders of the notes in the event that we experience significant adverse changes in our financial condition or results of operations;

limit our ability or the ability of any of our subsidiaries to incur additional indebtedness that is senior to or equal in right of payment to the notes;

restrict our ability or that of our subsidiaries to issue securities that would be senior to the common stock of our subsidiaries; or

restrict our ability to pledge our assets or those of our subsidiaries.

Therefore, you should not consider the provisions of these governing instruments as a significant factor in evaluating whether we will be able to comply with our obligations under the notes.

**Table of Contents****FORWARD LOOKING STATEMENTS**

This prospectus contains forward looking statements. These statements relate to future events or our future financial performance. We have identified forward looking statements in this prospectus using words such as anticipates, believes, could, estimates, expects, intends, may, potential, predicts, should, or will or the negative of such terms or other comparable terminology. These statements are based on our beliefs as well as assumptions we made using information currently available to us. Because these statements reflect our current views concerning future events, these statements involve risks, uncertainties, and assumptions. These risks, uncertainties, assumptions and other factors, including the risks outlined under Risk Factors, that may cause our or our industry's actual results, levels of activity, performance or achievements to be materially different from future results, levels of actual activity, performance or achievements expressed or implied by such forward looking statements.

Although we believe that the expectations reflected in the forward looking statements are reasonable, we cannot guarantee future results, levels of activity, performance or achievements. Moreover, neither we nor any other person assumes responsibility for the accuracy and completeness of such statements. We are under no duty to update any of the forward looking statements after the date of this prospectus to conform such statements to actual results, unless required by law.

**RATIO OF EARNINGS TO FIXED CHARGES**

The following table presents our historical ratios of earnings to fixed charges for the last five fiscal years and nine months ended September 30, 2003:

<b>Nine Months Ended September 30, 2003</b>	<b>Year Ended December 31,</b>				
	<b>2002</b>	<b>2001</b>	<b>2000</b>	<b>1999</b>	<b>1998</b>

<b>Ratio of earnings to fixed charges<sup>(1)</sup></b>					
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<sup>(1)</sup> For the nine months ended September 30, 2003, and for the years ended December 31, 1998, 1999, 2000, 2001 and 2002, no ratios are provided because earnings were insufficient to cover fixed charges.

These computations include us and our consolidated subsidiaries. Ratio of earnings to fixed charges is computed by dividing:

earnings from continuing operations before taxes adjusted for fixed charges, minority interest and capitalized interest net of amortization by,

fixed charges, which includes interest expense and capitalized interest incurred, plus the portion of interest expense under operating leases deemed by us to be representative of the interest factor, plus amortization of the debt issuance costs.

For our fiscal year ended December 31, 2002 earnings were inadequate to cover fixed charges by \$76.0 million. For the nine months ended September 30, 2003, earnings were inadequate to cover fixed charges by \$48.3 million

**HISTORICAL FINANCIAL INFORMATION**

With the commercial launch of Aldurazyme during the second quarter of 2003, we changed our presentation of the results of operations of our joint venture with Genzyme under the equity method. Previously, we recorded revenue to the extent that the services performed by us on behalf of the joint venture were funded by Genzyme. Costs incurred by us on behalf of the joint venture were recorded as operating expenses in the consolidated statements of operations. Equity in the loss of BioMarin/Genzyme LLC previously represented 50% of the joint venture net loss that related to costs not incurred by us on behalf of the joint venture.



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In the new presentation on the consolidated statements of operations, the equity in the loss of BioMarin/Genzyme LLC represents our 50% share of the joint venture's net loss. Costs incurred by us on behalf of the joint venture are included in the financial statements of the joint venture. This change in presentation had no effect on our loss from operations or net loss for any period. Both the prior presentation and the new presentation are acceptable under the equity method of accounting.

Our consolidated statements of operations for prior periods have been reclassified to conform to the new presentation. The following tables show the previously presented results of operations and the current presentation for the years ended December 31, 2002 and 2001, and the quarters ended March 31, 2002, September 30, 2002, December 31, 2002 and March 31, 2003. The effect of the reclassification on our consolidated statements of operations for the three and six months ended June 30, 2002 was presented in our Form 10-Q for the quarter ended June 30, 2003. The tables below are presented in thousands of dollars.

	Year Ended December 31, 2001		
	Prior Presentation	Reclassifications	New Presentation
Revenue from BioMarin/Genzyme LLC	\$ 11,330	\$ (11,330)	\$
Operating expenses:			
Research and development	44,914	(22,333)	22,581
General and administrative	6,718	(327)	6,391
In-process research and development	11,647		11,647
Equity in the loss of BioMarin/Genzyme LLC	7,333	11,330	18,663
Total operating expenses	70,612	(11,330)	59,282
Loss from operations	\$ (59,282)	\$	\$ (59,282)

	Year Ended December 31, 2002		
	Prior Presentation	Reclassifications	New Presentation
Revenue from BioMarin/Genzyme LLC	\$ 13,919	\$ (13,919)	\$
Operating expenses:			
Research and development	54,455	(27,168)	27,287
General and administrative	17,541	(670)	16,871
In-process research and development	11,223		11,223
Equity in the loss of BioMarin/Genzyme LLC	9,547	13,919	23,466
Total operating expenses	92,766	(13,919)	78,847
Loss from operations	\$ (78,847)	\$	\$ (78,847)

**Three Months Ended March 31, 2002**

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	<b>Prior Presentation</b>	<b>Reclassifications</b>	<b>New Presentation</b>
Revenue from BioMarin/Genzyme LLC	\$ 3,792	\$ (3,792)	\$
Operating expenses:			
Research and development	13,218	(7,466)	5,752
General and administrative	3,926	(118)	3,808
In-process research and development	11,223		11,223
Equity in the loss of BioMarin/Genzyme LLC	2,298	3,792	6,090
<b>Total operating expenses</b>	<b>30,665</b>	<b>(3,792)</b>	<b>26,873</b>
<b>Loss from operations</b>	<b>\$ (26,873)</b>	<b>\$</b>	<b>\$ (26,873)</b>

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	<b>Three Months Ended September 30, 2002</b>		
	<b>Prior Presentation</b>	<b>Reclassifications</b>	<b>New Presentation</b>
Revenue from BioMarin/Genzyme LLC	\$ 3,569	\$ (3,569)	\$
Operating expenses:			
Research and development	14,675	(6,937)	7,738
General and administrative	3,940	(201)	3,739
Equity in the loss of BioMarin/Genzyme LLC	2,350	3,569	5,919
<b>Total operating expenses</b>	<b>20,965</b>	<b>(3,569)</b>	<b>17,396</b>
<b>Loss from operations</b>	<b>\$ (17,396)</b>	<b>\$</b>	<b>\$ (17,396)</b>

	<b>Three Months Ended December 31, 2002</b>		
	<b>Prior Presentation</b>	<b>Reclassifications</b>	<b>New Presentation</b>
Revenue from BioMarin/Genzyme LLC	\$ 3,135	\$ (3,135)	\$
Operating expenses:			
Research and development	13,226	(6,044)	7,182
General and administrative	6,613	(226)	6,387
Equity in the loss of BioMarin/Genzyme LLC	2,438	3,135	5,573
<b>Total operating expenses</b>	<b>22,277</b>	<b>(3,135)</b>	<b>19,142</b>
<b>Loss from operations</b>	<b>\$ 19,142</b>	<b>\$</b>	<b>\$ (19,142)</b>

	<b>Three Months Ended March 31, 2003</b>		
	<b>Prior Presentation</b>	<b>Reclassifications</b>	<b>New Presentation</b>
Revenue from BioMarin/Genzyme LLC	\$ 3,496	\$ (3,496)	\$
Operating expenses:			
Research and development	17,758	(6,767)	10,991
General and administrative	3,024	(225)	2,799
Equity in the loss of BioMarin/Genzyme LLC	3,257	3,496	6,753
<b>Total operating expenses</b>	<b>24,039</b>	<b>(3,496)</b>	<b>20,543</b>
<b>Loss from operations</b>	<b>\$ (20,543)</b>	<b>\$</b>	<b>\$ (20,543)</b>

**USE OF PROCEEDS**

The selling securityholders will receive all of the proceeds from the sale of the notes and the common stock issuable upon conversion of the notes offered by this prospectus. We will not receive any proceeds. See Selling Securityholders for a list of those persons or entities receiving proceeds from the sale of the notes and the common stock issuable upon conversion of the notes.

The selling securityholders will not pay any of the expenses that are incurred in connection with the registration of the notes or common stock issuable upon conversion of the notes, but they will pay all commissions, discounts and any other compensation to any securities broker dealers through whom they sell any of the note or common stock issuable upon conversion of the notes.

In June 2003, we received net proceeds of approximately \$120.9 million from our sale of the notes. We intend to use the net proceeds for the commercialization of our first commercial product, Aldurazyme, development of additional manufacturing capabilities and facilities, preclinical studies and clinical trials for other product candidates, potential licenses and acquisitions of complementary technologies, products and companies, general corporate purposes, and working capital.

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**DESCRIPTION OF NOTES**

*The notes were issued under an indenture dated June 23, 2003, between us and Wilmington Trust Company, as trustee. The following summary of the terms of the notes, the indenture and the registration rights agreement does not purport to be complete and is subject, and qualified in its entirety by reference, to the detailed provisions of the indenture and the registration rights agreement. For purposes of this summary, the terms BioMarin, we, us and our refer only to BioMarin Pharmaceutical Inc. and not to any of our subsidiaries. References to interest shall be deemed to include liquidated damages, to the extent that we may be required to pay liquidated damages in the limited circumstances described in Registration Rights; Liquidated Damages.*

**GENERAL**

On June 23, 2003, we issued \$125 million aggregate principal amount of notes. The notes constitute unsecured indebtedness and are subordinated in right of payment to our senior indebtedness as described under Subordination of Notes. The notes are convertible into our common stock as described under Conversion Rights. Interest on the notes is payable semi-annually on June 15 and December 15 of each year, with the first interest payment to be made on December 15, 2003, at the rate of 3.50% per annum, to the persons who are registered holders of the notes at the close of business on the preceding June 1 and December 1, respectively. Unless previously redeemed, repurchased or converted, the notes will mature on June 15, 2008.

The notes were issued without coupons in denominations of \$1,000 and integral multiples thereof. The notes were initially issued as global securities in book-entry form. Payments in respect of the notes represented by the global securities will be made by wire transfer of immediately available funds to the accounts specified by the holders of the global securities. With respect to any notes subsequently issued in certificated form, we will make payments by wire transfer of immediately available funds to the accounts specified by the holders thereof or by mailing a check to each holder's registered address.

Holders may convert notes at the office of the conversion agent and may present notes for registration of transfer at the office of the registrar for the notes. The conversion agent and registrar for the notes initially will be the trustee.

Interest on the notes will be paid on the basis of a 360 day year of twelve 30-day months. No sinking fund is provided for the notes. The indenture does not contain any financial covenants or any restrictions on the incurrence of debt, the payment of dividends or the repurchase of our securities. In addition, the indenture does not provide any protection to the holders of the notes in the event of a highly leveraged transaction or a change in control, except and only to the extent described under Holders May Require Us to Repurchase Their Notes Upon a Repurchase Event and Consolidation, Merger and Sale of Assets, below.

**CONVERSION RIGHTS**

Holders of notes are entitled, at any time before the close of business on the date of maturity, subject to prior redemption or repurchase, to convert the notes or portions thereof (if the portions are \$1,000 or whole multiples thereof) into 71.3572 shares of common stock per \$1,000 of principal amount of notes. This rate results in an initial conversion price of approximately \$14.01 per share. Except as described below, the number of shares into which a note is convertible will not be adjusted for dividends on shares of our common stock. We will not issue fractional shares of common stock upon conversion of the notes and instead will pay a cash adjustment based on the market price of the common stock on

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the last trading day prior to the conversion date. In the case of notes called for redemption or subject to repurchase on a repurchase event, conversion rights will expire at the close of business on the business day immediately preceding the redemption date or repurchase date, as applicable.

Except as noted below, no payment or adjustment will be made for accrued interest on, or liquidated damages with respect to, a converted note or for dividends on any of our common stock issued on or prior to

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conversion. If a note is converted after the close of business on a record date for the payment of interest and prior to the next succeeding interest payment date, notes submitted for conversion must be accompanied by funds equal to the interest payable to the registered holder on the interest payment date on the principal amount of such notes submitted for conversion. We will then make the interest payment due on the interest payment date to the registered holder of the note on the record date. Notwithstanding the foregoing, any note submitted for conversion need not be accompanied by any funds if such note has been called for redemption on a redemption date that is after a record date for the payment of interest and on or before the day that is one business day following the corresponding interest payment date.

As soon as practicable following the conversion date, we will deliver through the conversion agent a certificate for the number of full shares of common stock into which any note is converted, together with any cash payment for fractional shares. For a discussion of the tax treatment of a holder receiving common shares upon surrendering notes for conversion, see Certain United States Federal Income Tax Considerations Conversion of the Notes.

We will adjust the conversion rate for:

dividends or distributions to all holders of our common stock payable in shares of our common stock;

subdivisions or combinations of our common stock;

distributions to all or substantially all holders of our common stock of certain rights or warrants entitling them for a period of not more than 60 days to purchase common stock (or securities convertible into common stock) at less than the current market price at the time (provided, that the conversion rate will be readjusted to the extent the rights or warrants are not exercised prior to their expiration);

the dividend or other distribution to all or substantially all holders of our common stock of shares of capital stock other than our common stock, evidences of indebtedness or other assets (other than cash dividends) or the dividend or other distribution to all or substantially all holders of our common stock of certain rights or warrants (other than those covered above) to purchase our securities;

cash dividends or other cash distributions to all or substantially all holders of our common stock in an aggregate amount that, together with

any cash and the fair market value of any other consideration payable in respect of any tender or exchange offer by us or any of our subsidiaries for our common stock consummated within the preceding 12 months not triggering a conversion rate adjustment; and

all other all-cash dividends or distributions to all or substantially all holders of our common stock made within the preceding 12 months not triggering a conversion rate adjustment,

exceeds an amount equal to 10% of the market capitalization of our common stock on the business day immediately preceding the day on which we declare the dividend or distribution; and

payments in respect of a tender or exchange offer by us or any of our subsidiaries for our common stock to the extent that the offer involves aggregate consideration that, together with

any cash and the fair market value of any other consideration payable in respect of any tender or exchange offer by us or any of our subsidiaries for our common stock consummated within the preceding 12 months not triggering a conversion rate adjustment; and

all other all-cash dividends or distributions to all or substantially all holders of our common stock made within the preceding 12 months not triggering a conversion rate adjustment,

exceeds an amount equal to 10% of the market capitalization of our common stock on the expiration date of the tender or exchange offer.

We will not adjust the conversion rate, however, if we make provision for holders of notes to participate in the transaction without conversion.



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No adjustment in the conversion rate will be required unless the adjustment would require a change of at least 1% in the then effective conversion rate; provided, that any adjustment that would otherwise be required to be made will be carried forward and taken into account in any subsequent adjustment.

We may at any time increase the conversion rate by any amount for any period of time, provided that the then effective conversion price is not less than the par value of a share of our common stock, the period during which the increased rate is in effect is at least 20 days or such longer period as may be required by law and the increased rate is irrevocable during such period. We are required to give at least 15 days prior notice of any increase in the conversion rate. We may also increase the conversion rate to avoid or diminish income tax to holders of our common stock in connection with a dividend or distribution of stock or similar event.

If we reclassify our common stock or are party to a consolidation, merger or binding share exchange, or a transaction involving the sale or other conveyance of all or substantially all of our assets, pursuant to which our common stock is converted into cash, securities or other property, at the effective time of the transaction, the right to convert a note into common stock will be changed into the right to convert it into the kind and amount of cash, securities or other property which the holder would have received if the holder had converted its note immediately prior to the transaction. This change could substantially lessen or eliminate the value of the conversion privilege associated with the notes in the future. For example, if we were acquired in a cash merger, each note would be convertible into cash and would n