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## **Firm thrives making drugs for rare conditions**

By Bernadette Tansey  
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BioMarin Pharmaceutical Inc. is having a good year. Sales of its three approved drugs are on the rise. Even better, the company is poised to become one of those rare biotech companies out there that actually makes money.

Yet the Novato company has also seen its share price slide by 17 percent in recent weeks, ever since a few doctors on an analyst's call speculated that its newest drug, Kuvan, would gain patients a bit more slowly than anticipated.

For a company like BioMarin, the maker of what are known as orphan drugs, every patient counts. Such companies develop treatments for illnesses so rare that they are often neglected by drug developers looking for bigger opportunities. In fact, when BioMarin was founded in 1997, people wondered how it would ever make a profit.

But the company, which was skirting bankruptcy four years ago, has found its footing, said Chief Executive Officer Jean-Jacques Bienaimé. "We've been growing much faster than the average biopharmaceutical company," Bienaimé said.

Although BioMarin's drugs serve no patient population larger than about 50,000 people worldwide, the company's market capitalization is now \$2.69 billion, more than a sixfold increase in the past three years.

Despite the market jitters over the rate of Kuvan's growth, BioMarin hasn't changed its sales projections for 2008. Most analysts said they were surprised by investor reaction to the doctors' comments, including the Cowen & Co. analyst whose June 23 interview with the physicians set off the share price slide. "We believe the recent weakness has been overdone and continue to recommend" BioMarin,' said Cowen analyst Phil Nadeau in a research note.

As a sign of its success, the Novato company has been mentioned as a possible takeover target because it has a growing revenue stream, plenty of cash, a pipeline of experimental drugs and expertise in manufacturing biologic drugs such as enzymes.

The company's gains were not easy to foresee when it tackled its first project, an "ultra-orphan" disease with a market the company now estimates at about 3,000 patients in the developed world. The devastating genetic disorder is called mucopolysaccharidosis I, or

MPS I. It distorts the bone structure and causes hearing loss, mental retardation and cardiovascular disease that is often fatal. BioMarin thought it could replace an enzyme missing in people with MPS I.

However, BioMarin's development costs soon exceeded \$100 million. "It still was hard to understand how it would work from a business perspective," said Dr. Emil Kakkis, the company's chief medical officer and a former UCLA professor whose research on MPS I helped lead to BioMarin's first product, Aldurazyme.

#### Role model

A host of factors have helped BioMarin become a prospering concern. It had a role model and early partner in Genzyme Corp. of Cambridge, Mass., a pioneer in the field of enzyme therapy. BioMarin also benefited from regulatory incentives for companies that take on rare diseases. Under the Orphan Drug Act, passed 25 years ago, such companies can receive fast-track drug approvals and more than seven years of U.S. market exclusivity. Europe has similar provisions.

One of the biggest factors behind BioMarin's financial growth, however, is the price of its products. Companies can charge premium rates for new drugs that improve treatment of rare illnesses. Aldurazyme costs an average of \$220,000 for a year's treatment. The drug helps patients with MPS I preserve the health of their lungs and their ability to walk.

"I'm not so interested in making expensive drugs," Kakkis said. However, he said, investors expect healthy returns for financing research, clinical trials and costly manufacturing plants. "You either have an expensive drug but you have a drug, or you have nothing," Kakkis said.

Since Aldurazyme was approved in 2003, BioMarin has brought two more drugs to market. Naglazyme treats mucopolysaccharidosis VI, or MPS VI, a disease related to MPS I that afflicts about 1,100 people in the developed world. In late 2007, the Food and Drug Administration approved Kuvan for another genetic disorder called phenylketonuria.

Kuvan is expected to drive BioMarin's near-term growth. About 50,000 people in the developed world suffer from phenylketonuria, with as many as 13,000 in the United States. But Kuvan is still an orphan drug with a small market, and the fortunes of orphan drug manufacturers can turn on the decisions of relatively few patients and their doctors.

However, Bienaimé is sticking with company predictions that 2008 Kuvan revenue will reach \$45 million to \$70 million, and net income will be \$28 million to \$40 million.

Each patient taking a BioMarin drug may contribute to the company's revenue for years, because the missing enzyme or other biological factor must be continuously replaced. The medicines are not cures for genetic disorders, but can only stave off some of the

damage caused by the diseases. Naglazyme costs an average of \$350,000 a year, and Kuvan costs an average of \$70,000 a year.

Most health plans don't balk at covering the cost of the drugs, analysts say. The very fact that diseases such as MPS I are so rare may help patients receive insurance reimbursement, said Leerink Swann analyst Joseph Schwartz. "Each insurance system has a very limited number of these patients," so the drugs don't add significantly to the insurer's total costs, he said. But the treatments save money if patients can avoid hospital stays, Schwartz said. BioMarin supports programs to help patients cover the cost of its medicines or their insurance co-payments.

Orphan drugs can bring in respectable revenue, and their development costs can be lower than for most medicines. While clinical trials of drugs for common diseases can involve thousands of patients, in rare disorders afflicting only a few thousand people, a trial may include fewer than 100 subjects, Bienaimé said. BioMarin has spent about \$350 million to \$400 million per drug in direct costs, he said.

BioMarin might someday tap into larger disease markets, such as cardiovascular disorders, if one of its new drug development projects succeeds. It is also developing a second drug for phenylketonuria called PEG-PAL, for those who don't respond to Kuvan.

But BioMarin is still working on ultra-rare illnesses. It recently announced a new program to develop an enzyme-replacement therapy to treat another form of mucopolysaccharidosis called MPS IVA or Morquio A Syndrome, which affects 1,100 to 3,000 people in the developed world.

Kakkis, a geneticist, said he is glad to see product revenue flowing back into research so he can try to develop more treatments for patients with rare inherited disorders.

"I'm finally in a position to do that," he said.

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