Company: BioMarin Pharmaceutical Inc. (BMRN)
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Over the past two weeks, we have worked on a (long/short) investment thesis in BioMarin Pharmaceutical Inc. ("BioMarin" or BMRN). The project was initiated based on (1) the Company's market capitalization of ≈ $600 million ($11.30 with 53.3 million shares on February 22; $130 million cash at year end), predicated on (2) expectations of clinical/regulatory success for its first product, Aldurazyme. Last May, I was bullish on the Company's private placement which raised $46.0 million from the sale of 4.87 million shares at $9.45, 16 percent off the prior day's close of $11.23. The placement included the issuance of 752,000 (15 percent) 3-year warrants which strike at $13.10 (117%).

Conclusion: *The data on BioMarin are mixed. The pivotal clinical trial missed one of two primary clinical endpoints and there may be product impurity (manufacturing) issues, both of which could delay the BLA filing or FDA approval. If BioMarin announces a delay in the BLA filing, the stock could lose 40 percent immediately. However, since I estimate a better than 90 percent chance of FDA approval within the following year, a significant drop may present a viable buying opportunity. If accepted for filing, I estimate a 70 percent chance of approval due to improved "guidance" from FDA, satisfactory (if not glowing) product safety and efficacy and a small, desperate patient population (perhaps half are children) with no viable alternative therapies. Significant stock price appreciation (assuming regulatory progress within the next 6 weeks) seems unlikely. Possible labeling restrictions (which shrink the potential market), reimbursement issues and profit sharing with Genzyme will keep pressure on the stock as well. Based on the current valuation and future earnings potential, I recommend a HOLD on BMRN.*

Introduction: Northern California-based BioMarin was originally a subsidiary of (Canadian) Glyko Biomedical, Ltd. (GBL) which in turn, had acquired Glyko, Inc., a carbohydrate analysis tool company. To complement Glyko's diagnostic/analytical expertise, BioMarin was formed in early 1997 to pursue therapeutic opportunities in carbohydrate enzyme related diseases. This class of some 40, rare genetic diseases are called mucopolysaccharidoses (MPS) or, alternatively, lysosomal storage diseases. Each is caused by the complete or partial absence of a single enzyme and affects fewer than 10,000 people worldwide. Therefore, each MPS may be treatable using recombinantly produced enzyme as a replacement therapy. The best known commercial example is Genzyme's Cerezyme, β-glucocerebrosidase, to treat Gaucher disease, which at $170,000/year/patient is expected to generate FY'01 revenues of ≈ $570 million.

In September 1998, the Company formed a 50/50 JV with Genzyme for worldwide rights to Aldurazyme to treat MPS-1. The deal is worth up to $30 million and included an $8.0 million equity stake in privately held BioMarin, an additional $10.0 million for equity at the IPO (July 1999) and a $12.1 million milestone upon FDA approval.

In the February 25 fiscal year-end press release, BioMarin announced that it had discontinued its Glyko, Inc. operating unit (≈ $2.7 million in 2001 revenues). Separately, in early February, the Company exchanged 11.4 million BioMarin shares for the 22 percent ownership held by GBL (no net change in share count).

Clinical Trial History:

BioMarin's first replacement enzyme is recombinant, human ∝-L-iduronidase to treat MPS-1 or Hurler disease. The Company has named the product *Aldurazyme*, a deficiency of which leads to the buildup of heparan sulfate and dermatan sulfate. Affecting roughly 3,400 people worldwide (1,000 in North America), the disease in its most severe form (40 percent of all MPS-1 patients; no native enzyme) results in short stature, hepatosplenomegaly (enlarged liver and spleen), corneal clouding and is typically fatal by age ten. Less severe forms of MPS-1 (due to the presence of residual enzymatic activity) are called Hurler-Scheie (50 percent of MPS-1; life expectancy of 50-60 years) and Scheie disease (normal life expectancy). The Company has completed two clinical trials.

Under former CEO and Founder, Grant Denison, BioMarin began in April 1998 what it described as a "pivotal" Phase 1/2, open label trial in ten patients at six US sites. The patients, six males and four females, ages 5-22 years old, included eight with Hurler-Scheie, one with Hurler and one with Scheie disease. All had some residual enzyme activity. Patients received weekly, IV infusions of enzyme, typically over a three-hour period; however, when infusion side effects such as hives, angioedema (swollen tongue) or hypoxemia were observed, the infusion rate was slowed, extending to four to six hours. Clinical data were collected but the BLA submission to FDA was planned to be based on improvements in *surrogate markers*, specifically (1) shrinkage of the liver and spleen and (2) reduced excretion of urinary glycosoaminoglycans (GAGs), which are elevated in diseased individuals.

In April 1999, BioMarin reported the results from this study (12mFU) showing statistically significant improvement in both endpoints; however, in November, FDA informed the Company that a larger trial, with *clinical endpoints*, would be required for BLA submission. In November 2000, Fredric Price replaced Denison as COB/CEO. In January 2001, BioMarin published its 12mFU results from the initial trial in the New England Journal of Medicine, a prestigious journal.

In December 2000, the Company initiated a randomized, DB-PC Phase 3 trial in 45 patients, ages 5-43 years old, 22 on drug, 23 on placebo with 26wFU. BioMarin proposed using a single PCE, improved Forced Vital Capacity (FVC; volume of air expired with maximum force), but FDA "strongly suggested" a second endpoint of improved performance on a 6 minute treadmill. Secondary endpoints of surrogate measurements similar to those in the first clinical trial were also collected. According to Mr. Price, the "most severe" MPS-1 patients were explicitly excluded from the trial, although apparently, one patient with Hurler was entered (placebo arm).

This past November, BioMarin reported so-called top line data from its pivotal trial. While the FVC improved in drug-treated versus placebo-treated patients ($p < 0.028$), comparative results from the treadmill test were suggestive of a positive, drug-related trend ($P = 0.066$), but not statistically significant. Other clinical observations (reported for the first trial) such as reduced sleep apnea and increased growth velocity (in prepubertal patients) were measured, but not reported.

Relevant Observations: **Positive**

1.*Safety*; Of the original 10 patients enrolled in the April 1998 trial, two have died from disease-related causes. Despite the burden of weekly, relatively time-consuming infusions, the remaining seven have continued on drug, providing good evidence of safety.

2.*Market adoption*; Less data are available for patients in the second study, which was completed for the last patient in late August. At that time, all of those in the placebo arm "crossed over" to active drug and all in the treatment arm opted to continue their infusions. So-called continuation studies typically provide only additional safety data; however, Mr. Price indicated that drug efficacy was also being monitored, though less frequently than during the formal trial. In fact, no patient ever dropped out of either trial and all 52 continue on drug, suggesting the drug's efficacy as perceived by patients and their remarkable tolerability of an onerous dosing regimen.

3.*Secondary endpoints*; While generally insufficient for FDA approval, the reduction in urinary GAGs and improvement in hepatosplenomegaly clearly demonstrate Aldurazyme's sustained activity. Coupled to the single PCE with statistical significance and relative safety (since infusions only occur in a medical setting), the aggregate clinical and biochemical data may be sufficiently robust to support approval.

Relevant Observations: **Negative**

1.*Intellectual property*; Transkaryotic Therapies (TKTX) has licensed two patents for recombinant human iduronidase, one of which has been rejected in Europe. Neither has been contested in the US, but it appears likely that BioMarin will need to reach an agreement with TKT prior to launching US sales, if approved.

2.*Company guidance*; A BLA submission for Aldurazyme has been delayed at least twice before. In November 1999, after agreeing to FDA's request for a second clinical trial, the Company announced its plan to file a BLA by YE'00. In a June 2001 S-3 filing, BioMarin said it expected to file the BLA by YE'01. On February 22, Mr. Price suggested that the filing may be delayed a little from Q1/02, as currently expected.

3.*Negative signaling*; In December, BioMarin raised gross proceeds of over $96 million from a secondary offering (8.05 million shares at $12.00). In all of 2001, the Company raised ≈ $156 million, including a private placement for $46 million and $13.4 million drawn against an equity line of credit. Sometimes, such aggressive financing suggests expectations for future stock price deterioration.

4.*Redirection*; During the February 22 meeting, Mr. Price pitched BioMarin as "more than the Aldurazyme company," emphasizing the significant market opportunity for its recently acquired heparinase (Neutralase) to reverse heparin-based anticoagulant therapy during CABG. In fact, this enzyme previously failed in a Phase 3 trial for this indication, though enzyme dosing was significantly lower than that used in a previous Phase 2 trial. Such redirection may suggest an Aldurazyme discount; but, in fact, the Company's market capitalization fully rests on this product's success. A clinical/regulatory stumble will prove immediately devastating.

5.*Corporate partner*; Despite its reputation (and $10 billion market cap. (10x LTM revenues) to match), Genzyme has only developed one recombinant product. Ceredase, which was isolated from human placentas, was approved in April 1991 to treat Gaucher disease, an MPS similar to Hurler disease. In May 1994, the recombinant enzyme, called Cerezyme, was approved. Surprisingly, in June 2000 Genzyme filed a BLA for its second MPS replacement enzyme, α-galactosidase, called Fabrazyme, to treat Fabry disease. In December, FDA rejected the BLA (despite its having Orphan Drug, Fast-Track and Priority Review (6 month) status) asking for more data (clinical, not surrogate endpoints) including an additional clinical trial. Also, last August, Genzyme acquired privately held Novazyme for $138 million. Novazyme was a direct competitor to, but 18 to 24 months behind, BioMarin.

6.*Statistics*; Although the calculation of "p values" accounts for small populations, *true* clinical value may be difficult to ascertain due to the inherent variability in the biology of a disease. This is especially true when testing a drug over a relatively short period (e.g., 26 weeks) for a disease like Hurler-Scheie or Scheie which progresses over decades. BioMarin's PCE of FVC may have met statistical significance essentially based on the results of one or two patients. FDA may require larger and/or longer clinical trials. It is also unclear whether FDA will clear a drug when only one of two PCEs are hit.

7.*Manufacturing*; Minor contaminants and/or microheterogeneity in the purified enzyme preparation can add up, leading to immunogenicity, possibly severe, especially when 20 to 40 mg of enzyme are infused weekly, for life. The original preparation was produced at Harbor-UCLA and was clearly impure, since all ten patients developed antibodies to CHO cell proteins. Four patients also transiently developed (non-neutralizing) antibodies to the recombinant enzyme. All of these patients were tested with, then switched to material produced at the Company's Galli Drive facility. If the purification process has not improved, then an FDA rejection could result in the need for a new process and, therefore, an additional clinical trial, most likely as a "cross-over" of currently treated patients to the new formulation. It is possible that, at this time, FDA has already suggested this path and recommended that the company not submit its BLA until the cross-over study is complete.

8.*"Labeled" use*; Aldurazyme has not been tested in Hurler patients deficient in any endogenous iduronidase (so-called "null genotypes"). These are (1) the most severe cases of MPS-1 with the greatest need for enzyme and (2) those most likely to mount a protective immune response to this "foreign" protein. If approved, Aldurazyme's label may require genotyping and exclude null genotypes (mostly Hurler patients). Thus, the North American market may turn out to be less than 500 patients.

9.*Personnel*; Recently, Jeremy Price, son of Chairman and CEO Fredric Price, was hired as Manager, Investor Relations. Any nepotism suggests less than a pure meritocracy.

Events: There are two events relevant to BMRN within the next six months.

1.*BLA Submission*; The absence of any mention of BioMarin's BLA submission plans in its February 25 fiscal year-end press release has put pressure on the stock. The Company's 10-K should be available around March 20. Unfavorable discussions with FDA (held during this quarter) may be disclosed at that time.

2.*Fileable notice*; If BioMarin does submit its BLA, FDA will have 60 days to accept it for filing. The Company has disclosed (personal communication) that it plans to petition FDA for priority review (6 months instead of 10). A "refuse-to-file" letter (like Imclone's) would be rare, unlikely and, of course, catastrophic.