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Adolor: A Small Stock to Watch

by: Smith On Stocks

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Adolor (ADLR) as a Stock

While I am currently neutral on Adolor, it is a stock that I am watching closely. To become more positive, I need to gain more confidence that its lead drug Entereg, which has had a slower-than-expected sales ramp-up since its introduction in 3Q 2008, can grow from a current run rate of $30 million in sales to $100 million in the next five years. I am also awaiting phase II results from ADL5945 in 3Q 2011, which potentially has greater promise than Entereg in the opinion of management. Success in this trial could create considerable investor interest and potentially a meaningful upside move in the stock. It could also lead to a partnering deal, which is essential to develop ADL5945.

Adolor Targets Opioid-Induced Constipation

Opioid analgesics are the most important class of analgesics used for treating severe pain which occurs in post-surgical/chronic pain, trauma, dental extraction and many other settings. The most well-known naturally-occurring opioids are morphine and codeine, which are found in the resin of the opium poppy. There are also a large number of semi-synthetic opiates which are derived from natural opiates and include hydromorphone, oxycodone and buprenorphine. There are also synthetic agents such as fentanyl and tramadol.

In the U.S., it is estimated that there are 57 million acute users of opioids and 12 million chronic users. This is a huge market in which there were 272 million opioid prescriptions written in 2009; the market growth has been about 4% per year. Opioids bind to central μ-opioid receptors in the brain to provide pain relief. However, they also bind to μ-opioid receptors in the intestines, and this causes the side effect of constipation. While this is a problem for acute users (post-surgical, for example), it is more of an issue for the chronic users. Adolor believes that 50% of chronic opioid users, or over 6 million people, suffer from constipation. This is a market with great unmet need, and constitutes a U.S.-addressable market of as much as $6 billion if these estimates are correct.

Adolor has been focused on this opioid-induced constipation opportunity since its inception and formed a partnership with Glaxo (GSK) in 2002 that led to the development of its lead drug, Entereg (alvimopam). This partnership was the first to focus on this market opportunity.

Entereg

Clinical progress was excellent with Entereg, and Adolor and Glaxo were moving rapidly toward commercialization. Enthusiasm for Entereg's potential led to a market capitalization of over $1 billion for Adolor in 2006. However, Entereg hit a roadblock when a safety study showed a significant imbalance in the incidence of myocardial infarctions in the Entereg arm in comparison to the placebo arm. Specifically, there were seven myocardial infarctions in the Entereg arm and none in the placebo patients.

This potential link of Entereg to myocardial infarction was a total surprise and remains unexplained. There is no known mechanistic link and no evidence from the literature to suggest that Entereg could cause myocardial infarctions. Some have speculated that opioids are cardioprotective and that Entereg might block that effect, but views on this are mixed. This may have been a chance occurrence in the trial, but it was sufficient to prevent the use of Entereg in chronic opioid-induced constipation. However, Adolor and Glaxo were still able to gain approval for Entereg by moving from the chronic opioid-induced indication to a niche indication for acute use in bowel resection patients.

If Entereg had been approved for chronic opioid-induced constipation, it might have had $1 billion of potential. However, in its approved indication, I think that $100 million might be a more realistic goal. Importantly, this would generate about $30 million of annual cash flow. The addressable market for Entereg is about 500,000 patients in the

U.S. who undergo bowel resection surgery each year. Entereg is priced at about $70 per capsule and is indicated for twice-per-day use, with a limit of 15 capsules per patient. The average patient consumes 8 ½ capsules per course of therapy. This results in an addressable market of $300 million, and I am looking at a market share of 33% to reach $100 million.

The FDA mandated a rigorous REMS program which required educating the hospital staff, limiting the number of capsules per patient to 15 and prohibiting dispensing the product outside of the hospital. Adolor and Glaxo have labored under the burden of the REMS program. They have to register a hospital in the REMS program before Entereg can be sold. They now have registered 1,150 of the 1,400 most important bowel resection surgery hospitals. The product is on formulary in 745 of these. Hospitals are reimbursed under DRGs. The company must convince the hospital that the cost saving created by Entereg in terms of reducing the length of hospital stays (a little over one day) is worth the price of therapy, which on average is around $600. Gaining reimbursement has also been a slow process.

The original agreement with Glaxo called for Adolor to co-promote. Surprisingly, Glaxo elected to market Entereg for the small niche indication even though the potential $100 million of sales is a rounding error in Glaxo's total sales of $46 billion. Glaxo has 200 reps selling this product in the U.S. and Adolor has 25. Profits are shared on a 50/50 basis.

There continues to be speculation that Glaxo will return Entereg to Adolor. I would be positive it this were to occur. There are 1,400 hospitals that perform 80% of the total bowel resection surgeries. If Glaxo were to give the product back, Adolor would probably add 30 to 40 salesmen and could cover most of this market. It might also contact other companies with hospital-targeted sales forces that might be interested in a co-promote such as Cumberland (CPIX), Cubist (CBST) and potentially Cadence (CADX). To completely control Entereg marketing would be a major positive for Adolor, in my judgment.

Entereg's Market Protection

It is tough being the first product in a new category and going through the REMS process and reimbursement. On the other hand, it is a barrier to entry for other products. In addition, the patent covering Entereg runs through 2020. This suggests a nine-year period of exclusivity, which is highly positive.

Adolor Again Targets Chronic Opioid-Induced Constipation

Management believes that while Entereg is important, the most important value driver of the company may be a new product for chronic opioid-induced constipation. Glaxo has elected not to participate in this program, and Adolor has decided to go it alone.

Adolor put two such products into phase I clinical trials in early 2010. These were ADL-5945, which was in-licensed from Eli Lilly (ELY), and the internally developed ADL-7445. Adolor elected to move ADL-5945 forward into a phase II trial, the results of which will be available in 3Q 2011. These results are of much importance to the company. Success would hold the promise of a drug with much greater potential than Entereg. It might also lead to a critically needed partnering deal. The development program for ADL-7445 could cost about $50 million from the end of phase II thorough the filing of the NDA. Given the current $64 million market valuation of Adolor, this is a daunting challenge without a partner.

Adolor has already conducted the types of studies that will be required for ADL-5945 when it was developing Entereg. It has considerable expertise. It also received an SPA for Entereg in chronic opioid-induced indications that gives a clear roadmap to establishing acceptable primary endpoints in a phase III trial for ADL-5945. Assuming success in phase II, the phase III trial could start in early 2012 and an NDA filing would be targeted for late 2014. There will be little or no news until the initial efficacy results of phase III are reported.

Financial

The company had $53.6 million in cash at the end of 3Q 2010. It has reduced its burn to $25 million per year, which gives it about two years of cash. Management hopes that a partnering deal for ADL-5945 could bring in a significant upfront payment that would put it in an enviable cash position which could sustain it through to profitability arising from Entereg sales. Of course, this is contingent on a lot of unknowns -- foremost of which is whether the data will be positive. Behind this is whether the data will drive a partnering deal and what the terms of that deal might be.

Competition

Adolor created the chronic opioid-induced constipation category, but the setback with Entereg has enabled Nektar (NKTR) and its partner AstraZeneca (AZN) to become the development leaders. They did a huge deal on September

21, 2009 based on phase II data for NKTR-118 and NKTR-119. Astra-Zeneca paid an upfront milestone of $125 million and committed to total potential milestones of $995 million. Interestingly, this is the same stage of development as ADL-5945 will be in at the completion of their phase II trial in 3Q 2011. Some Nektar investors are concerned that the beginning of phase III has not yet been announced.

Relistor of Progenix (PGNX) also competes in this market and, like Entereg, is also an approved product in an even smaller niche market. Relistor is currently only available in a subcutaneous dosage form that is not appropriate for the market. Progenics is trying to develop an oral formulation, but progress has been slow.

Alkermes (ALKS) has just announced positive phase II results for ALKS 37 in a phase II trial involving 87 patients. The phase III trial will begin in mid-2011. Theravance (THRX) also has a program in this area.

Unlike five years ago when Adolor and Glaxo were the pioneers in this category, Adolor is no longer the clear leader in this space. NKTR-119 claims this title. However, Adolor is not that far behind and, assuming everything goes right in the development of both drugs, ADL-5945 could be commercialized only a year or two behind NKTR-119.

Disclosure: I have no positions in any stocks mentioned, and no plans to initiate any positions within the next 72 hours.

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