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Report: A Brief History of Systemic Lupus Erythematosus at Immunomedics (IMMU)
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Volatility is one hallmark of biotechnology stocks. Therefore, it behooves investors to recognize the limits of a stock's sudden pop by understanding the historical context under which a company releases news. The recent activity in Immunomedics provides an excellent example of how, at investors' peril, a stock's dramatic rise effectively ignores a company's past. On August 27, 2009, Immunomedics (and partner UCB, S.A., Belgium) issued a press release reporting "promising" Phase 2b data for epratuzumab in moderate-to-severe systemic lupus erythematosus ("lupus"). The stock closed up 61% to a five-year high of $6.84 on 30 times the average daily volume. A brief review of lupus at Immunomedics should help put this news into its proper perspective.

Conclusion

Perhaps it was fortuitous timing that five weeks earlier Human Genome Sciences (HGSI) announced positive results in its first of two Phase 3 trials of Benlysta for lupus (lifting its stock 277% to $12.51). HGSI's news certainly provided a tail wind to Immunomedics' choice to announce positive results from UCB's Phase 2b trial of epratuzumab in lupus. However, given Immunomedics' past performance, long history and sub-par return on investment, investors should have been a bit more skeptical of the Company's news release.

Knowing that 90% of all biotech companies are not profitable and that the time, expense and uncertainty of drug development stack the odds against success, investors would do well to remember past performance. Take good notes. Sadly, for most of these companies, past performance is a good proxy for future results.

Company Background

Founded 27 years ago, New Jersey-based Immunomedics is still led by its Founder David Goldenberg, MD, currently Chairman and Chief Scientific Officer and by his wife, Cynthia Sullivan, who is President and CEO. For fiscal year end this past June, the Company reported $27.4 million of cash and equivalents, no debt, product revenues of $3.5 million plus license fees and other revenues of $25.5 million. The accumulated deficit since inception (July 1982) is $240 million. On the day of Immunomedics' news, the company had 75.2 million shares outstanding. The stock closed at $6.84, giving Immunomedics a market capitalization of about $515 million.

The Company has no FDA approved drugs but does have four, simple medical devices (approved under 510(k) requirements) used as diagnostics. The first diagnostic was approved in 1986 and the fourth in 1998, but diagnostics are not the Company's focus or area of expertise.

Epratuzumab for Lupus

History

In July 1997, Immunomedics licensed Repligen's humanized monoclonal antibody, called LL2 (later called Lymphocide, epratuzumab) targeting the CD22 marker on B-cells. The Company expected the antibody to be useful in treating Non-Hodgkin's Lymphoma (NHL). A Phase 3 trial was begun in September 2000 and, within three months, Immunomedics had partnered with Amgen on this project. In early 2003, Amgen halted the trial saying that it was "not commercially interesting." In a November 2003 press release, Immunomedics noted that it was in "advanced discussions" with Amgen concerning the return of epratuzumab rights. Immunomedics' stock dropped 53% to $3.38 on 15.2 million shares. In April 2004, Amgen returned the drug to Immunomedics.

Immunomedics' Phase 2 Trial in Lupus

A month later, in May 2004, the Company reported for the first time, clinical data for epratuzumab in lupus patients. These interim results were from a Phase 2 study in 11 patients treated for moderate lupus. There were no serious adverse events, no infusion reactions and no anti-epratuzumab antibodies detected. Further, there was "initial evidence of symptomatic improvement." The complete data set for this study was published in April 2006 (see http://arthritis-research.com/content/8/3/R74). This was Immunomedics *only* Phase 2 trial of epratuzumab for lupus and was the only clinical study on which the Company later based it's two Phase 3 studies. The Phase 2 study was a single arm, open-label, non-randomized trial and was conducted on *14 patients* (only 12 received all four infusions) at a single site, in Berlin, Germany. Every two weeks patients were infused with epratuzumab at 360mg/meter² for a total of four infusions (weeks 0, 2, 4, and 6). This dosage and regimen were based on data from Immunomedics' earlier studies in NHL. Patients were evaluated using the BILAG[1] system at week 6, then at weeks 10, 18 and 32 (the six-month follow-up post-treatment).

To most observers, a single, 14-patient trial is simply too small a study on which to predicate Phase 3 studies. Almost by definition, the pivotal trials suitable for FDA registration will be large (i.e., expensive), randomized, double-blinded, placebo-controlled and conducted at numerous clinical sites. There's an old adage in the clinical development community that goes:

> "You do Phase 1 and Phase 3 trials for the government. The Phase 2 trials are your real experiments."

Unfortunately, rather than performing careful, well-designed Phase 2 "experiments," Immunomedics rolled the dice and jumped into two Phase 3 trials of epratuzumab for lupus.

Immunomedics' Phase 3 Trials in Lupus

In June 2005, Immunomedics announced the initiation of two, Phase 3 trials of epratuzumab for lupus. Designed as randomized, double blind, placebo-controlled studies to be conducted at more than 60 sites around the world, the first trial was named ALLEVIATE A (Alleviate Lupus Affliction with Epratuzumab and Validate its Autoimmune Safety and Efficacy - Author's inference of the acronym's origin). Astonishingly, this trial was to enroll 510 patients with *severe* lupus, despite Immunomedics never having tested, under a clinical trial, a single severe lupus patient previously[2]. The second trial, ALLEVIATE B was scheduled to test 300 patients with *moderate* ("active") disease, similar to those in the Ph 2 trial described above. All patients were to be randomized between their current standard of care plus either epratuzumab or placebo. And, for both pivotal trials, the primary clinical endpoint was a statistically significant, clinically relevant improvement in the BILAG score, evaluated at 24 weeks.

[1] For more information on BILAG and clinical trial designs for lupus, see FDA's March 2005 Guidance Document: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072063.pdf

[2] On March 28, 2005, one patient with severe, Rituxan resistant lupus was treated with, and responded to, epratuzumab. The drug was provided under the FDA's compassionate use program.

Roughly a year later (May 2006), Immunomedics partnered with UCB, an 80 year-old Belgian firm which, by 2004, had evolved, mostly by acquisitions, from a specialty chemical firm into a respected, biotech pure-play. The $183 million deal included a $38 million up-front payment plus milestones to Immunomedics in exchange for worldwide rights to epratuzumab for all autoimmune indications. The May 10 press release noted that not only would UCB pay all development costs going forward, but also "UCB plans to escalate activity in the ongoing Phase 3 studies..." Sometimes plans change.

About four months later (September 26, 2006), the FDA put the trials on clinical hold, based on UCB's findings of the potential for sterility problems during epratuzumab's fill-and-finish process. Immunomedics filed an 8-K with the SEC, but there was no press release. However, within 60 days (November), the holds were lifted and announced in an Immunomedics' press release. Thus, within eight months of becoming partners, UCB's plans for epratuzumab had changed dramatically. In January 2007, both trials were "suspended." Six weeks later, both trials were terminated.

Immunomedics "announced" the suspension of the Phase 3 trials in its 10-Q filing of February 9, 2007. They also reported that UCB appeared likely to change both the manufacturing process and the clinical trial design. The lag between when nominally adverse events occurred and when Immunomedics conveyed this information to investors is disconcerting. However, in addition to press releases and SEC filings, investors often have access to clinical trial progress at the NIH-sponsored website, ClinicalTrials.gov. For example, for the history of ALLEVIATE A, please see http://clinicaltrials.gov/archive/NCT00111306.

UCB's Phase 2b Trial in Lupus

By February 2008, less than a year after UCB terminated the Phase 3 trials, UCB initiated a full-blown Phase 2b trial of epratuzumab in lupus. *The study design was a role model for robust clinical development.* With plans to enroll 210 patients (227 were actually enrolled) diagnosed with both moderate and severe lupus, the study was double-blinded, placebo-controlled and dose ranging (200mg to 3,600mg total) with study drug infused either weekly or every two weeks for a four-week course of therapy. The primary clinical endpoints were evaluations using both BILAG and a well-established disease activity index called SLEDAI, both at week 12. Patients were enrolled from some 55 sites including 19 in the US, eight in Brazil and six in India. Enrollment was completed this past March and the trial concluded in August.

Immunomedics' press release on August 27 does not do justice to this clinical trial. For example, it is worth highlighting that even though the study enrolled 227 patients, they were spread across six arms, five different dosages of epratuzumab plus a placebo group for each regimen. Although the patients were mixed with respect to disease severity (70:30 severe: moderate), it is unclear if that ratio was maintained for each dosage. Finally, from a clinical perspective, stating that the so-called "treatment advantage of epratuzumab over placebo reached 24.9% at week 12" is virtually meaningless. What does this mean? Was this difference statistically significant? A brief note in the next day's Wall Street Journal suggested that the result was not statistically significant. Still, Immunomedics' press release must have left some investors puzzled.

One especially churlish interpretation could be that patients receiving a total dosage of 3,600mg of epratuzumab did no better or worse than those receiving 200mg. Thus, all drug cohorts may have been aggregated and compared, as a group, to the placebo arm. This is highly unlikely (plus the absence of a dose-response effect would be especially worrisome) and investors should look for future presentations by Immunomedics and UCB to clarify exactly what was observed. This year's annual meeting of the American College of Rheumatology runs from October 17 through October 21. It's the ideal forum for Immunomedics and UCB to present the full data set from this study.

Recent News

On August 31, 2009, Immunomedics filed an S-3 registration to sell 20 million shares and three million warrants. In this document, the Company makes the following note. "Subsequent to June 30, 2009, UCB relieved us of our remaining obligation to supply UCB with any further supplies for SLE." UCB has indicated that it expects to meet with the FDA next spring, or earlier, to discuss the Phase 3 design. A key decision, often overlooked by analysts, is that the manufacturing protocol of the active drug substance used in a Phase 3 trial should be relatively "locked down." Small changes to the process may be tolerable (e.g., using less antibiotic in a fermentation), but large changes (e.g., changing the amino acid sequence of a protein) must be avoided. Because products originating from biological processes are more complex chemically than small molecules, there is elevated potential for increased variability in the final product. The agency wants to ensure that what was tested in Phase 3 is what will be used commercially. UCB is experienced in biologics manufacturing for commercial use. Immunomedics is not. By taking control of epratuzumab's manufacture now, UCB mitigates the potential for future risk.