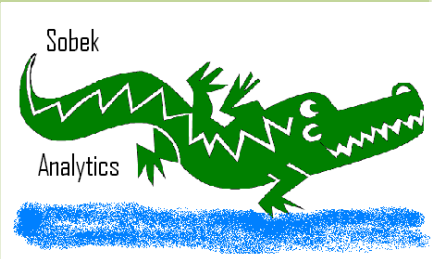


Benlysta: Hype or Hope?

March 10th Key Date

Human Genome Science's (HGSI) has an important date with the FDA on March 10th as they should hear whether or not Benlysta will be granted marketing approval for systemic lupus erythematosus (SLE). Benlysta offers an interesting choice for the FDA as no new drug has been approved for SLE in over 50 years but the benefit seen with Benlysta has been marginal. In fact, while Benlysta leads to statistically significant improvements in the primary endpoints of the BLISS-52 and BLISS-76 trials at week 52 that benefit appeared to wane by week 76 in the BLISS-76 trial. To add to the contrary signals, on November 16th, 2010 the Arthritis Advisory Committee of the U.S. Food and Drug Administration (FDA) voted 13 to 2 to recommend that the FDA approve BENLYSTA® (belimumab) for the treatment of autoantibody-positive patients with active systemic lupus erythematosus (SLE). So what is an investor to make of these contradictory signals? We can boil this down to two related, but different questions. First, does Benlysta offer a clinically meaningful benefit? Second, is that benefit large enough to justify FDA approval?

Take Home Points

Benlysta tackles an exceptionally difficult disease given its inherent heterogeneity. While it would be nice to have crystal clear efficacy signals, that is likely too high of a hurdle. That being said, the BLISS-52 and BLISS-76 demonstrate a clinical benefit for patients that likely also has an important quality of life improvement for the patients. As such, it is likely that the FDA will grant Human Genome Science marketing approval, although not guaranteed. I would place the odds at 70% approval and 30% some form of non approval.

Contents

Measuring Improvement

In the trials the primary efficacy endpoint was improvement in the Systemic Lupus Erythematosus Responder Index (SRI) at week 52 (reduction ≥4 points in SELENA-SLEDAI score; no new British Isles Lupus Assessment Group [BILAG] A organ domain score and no more than 1 new B organ domain score; and no worsening [<0・3 increase] in Physician's Global Assessment [PGA] score) versus baseline. The BLISS-76 trial was continued for an additional 24 weeks to get a sense of the durability of these improvements. So what exactly does this endpoint mean?

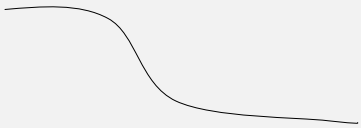
Given the heterogeneity of the disease, it is difficult to get a single score of the severity. Rather there are a set of measures that have been used and the SRI is essentially a compilation of these various measures. So in order to be considered a responder, a patient needs to cross a series of hurdles (seen in the previous paragraph). The advantage of having a stringent measure of success is that it is good at filtering out non-responders or those that have achieved only minor benefits.

As such, the trial is designed to see if patients treated with Benlysta improve at a greater rate than those not on Benlysta. This improvement, however, needs to be statistically significant (meaning unlikely to be random).

The BLISS-52 trial results (recently published in Lancet) were quite positive. The SRI rate of improvement was higher than placebo and clearly statistically significant (p-value of 0.0006).

The Problem with Degenerative Diseases

SLE is a degenerative disease and thus offers an additional layer of complications in figuring out whether or not a drug is providing a clinically meaningful effect. One could imagine that most degenerative diseases follow an S-curve over time where the degeneration is slow at first, picks up steam in the middle, and then slows towards the end (see figure below for a general sense).



If a drug (like Benlysta) is able to move patients up the steep part of the curve, then there is more room to degenerate. So over the long-term unless a treatment cures the disease, all patients will eventually converge. So it is not completely surprising to see the benefit moderate at week 76 as compared to week 52. This does not mean Benlysta does not work; rather, it is fighting a tough degenerative disease at the steep part of the curve.

Does It Work?

The BLISS-52 trial results (recently published in Lancet) were quite positive. The SRI rate of improvement was higher than placebo and clearly statistically significant (p-value of 0.0006). In addition, a dose response was noted where those receiving the 10-mg/kg dose had statistically significant improvements in all SRI categories whereas the 1-mg/kg dose only saw statistically significant improvements in two of the three categories. The improvements were relatively rapid with the first indications occurring as early as 16 weeks. An additional benefit of Benlysta was a decreased need to use prednisone, where the last 36-weeks of the study the placebo group used prednisone at higher levels (statistically significant). So overall, it looks like a clear cut benefit for Benlysta.

The problem is that the BLISS-76 trial was extended and the top-line results did not show a statistically significant improvement at week 76. The SRI at Week 76 were 38.5% for the 10 mg/kg dose, 39.1% for the 1 mg/kg dose, and 32.4% for the placebo (p-values of=0.13 and p=0.11 for 10 mg/kg and 1 mg/kg belimumab, respectively vs. placebo). Compared to the Lancet article, the response rates for all three doses were lower (58% for the 10 mg/kg dose, 51% for the 1 mg/kg dose, and 44% for the placebo) but the rate for the Benlysta patients decreases at a faster rate. So what does one make of this change? First, the Benlysta patients still showed an improvement compared to placebo. Second, p-values of 0.13 and 0.11 may not be statistically significant but are not horrible. Third, benefits still appeared underneath the top-line "miss". In particular,

--The proportion of patients with a reduction in SELENA SLEDAI score of at least 4 points was 41.4% for the 10 mg/kg dose, 42.1% for the 1 mg/kg dose, and 33.8% for placebo (p=0.066 and p=0.049 for the 10 mg/kg and 1 mg/kg doses, respectively vs. placebo).

--At week 76, the mean percent reduction in SELENA SLEDAI score was 37.0% for the 10 mg/kg dose, 36.1% for the 1 mg/kg dose, and 27.8% for placebo (p=0.01 and p=0.03 for the 10mg/kg dose and 1 mg/kg doses, respectively vs. placebo).

A final note to make is that this is a progress disease, which adds an additional layer of complications (see sidebar). For complete top-line results see the HGSI press release.

Whither the FDA

It is difficult to give a clear recommendation as to the decisions of the FDA because there are multiple factors that go into their choices outside of the science. Regardless, a couple of facts can be established. First, it has been over 50 years since a new treatment has been approved for SLE. Second, Benlysta provides a statistically significant benefit at week 52, which is the primary endpoint per the SPA. Third, the benefit of Benlysta is not constant as can be seen by the decreased benefit achieved at week 76. While the ideal drug would offer improvements across the time periods, I believe that it is likely that the FDA will approve the drug based on the benefits that had been observed and the clear unmet medical need for SLE patients.

Of course, there is always risk when looking at FDA decisions so it is not 100% clear that the FDA will approve Benlysta. I do feel that the odds are in favor of approval and place them at 70% approval and 30% non-approval. The non-approval could include a need for more testing or extensions of current trials.

These percentages derive from my interpretations of the trial results and belief that SLE is an important unmet medical need that the FDA would want to see filled. Benlysta is not perfect but a drug does not have to be perfect but simply a significant improvement from current treatments. I think the data supports that view.

Findings from the Lancet Article-

Direct quotes from first page:

Background Systemic lupus erythematosus is a heterogeneous autoimmune disease that is associated with B-cell hyperactivity, autoantibodies, and increased concentrations of B-lymphocyte stimulator (BLyS). The efficacy and safety of the fully human monoclonal antibody belimumab (BLyS-specifi c inhibitor) was assessed in patients with active systemic lupus erythematosus.

Interpretation Belimumab has the potential to be the first targeted biological treatment that is approved specifically for systemic lupus erythematosus, providing a new option for the management of this important prototypic autoimmune disease.

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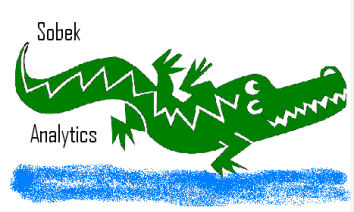

Reference to HGSI Press Releases

HUMAN GENOME SCIENCES AND GLAXOSMITHKLINE ANNOUNCE TOPLINE 76-WEEK RESULTS OF PHASE 3 TRIAL OF BENLYSTA™ IN SYSTEMIC LUPUS ERYTHEMATOSUS

HUMAN GENOME SCIENCES AND GLAXOSMITHKLINE ANNOUNCE PUBLICATION OF BLISS-52 PHASE 3 STUDY RESULTS FOR BENLYSTA® IN THE LANCET

HUMAN GENOME SCIENCES AND GLAXOSMITHKLINE ANNOUNCE POSITIVE RESULTS IN SECOND OF TWO PHASE 3 TRIALS OF BENLYSTA™ IN SYSTEMIC LUPUS ERYTHEMATOSUS

Disclaimer

I am not a certified financial analyst. All the information provided in this report is my interpretation and may contain errors. Please, do not invest based solely on my opinions as it is critical for all investors to conduct their own due diligence and invest in ways that best fit their own needs. In addition, I have no position in HGSI. In addition, it is important to note that this is not a recommendation to buy or sell HGSI. Investing in HGSI would require an analysis of all the risks and benefits that are outside of those discussed in this report. For instance, approval of Benlysta may already be priced in and so the price per share may not react as one would expect on approval (or it may not be priced in). Regardless, this report is design to be part of a due diligence effort and should be read in that context.