



## **Belimumab for Systemic Lupus Erythematosus**

Belimumab (Benlysta™) was approved by the FDA on March 8, 2011 for the reduction of disease activity in adult patients with active, autoantibody positive systemic lupus erythematosus who are receiving standard therapy. It is the first drug to be specifically approved for treating SLE in more than 50 years. The approval was based on two pivotal phase III trials, along with safety data from these trials and a phase II trial with an open-label extension.

Belimumab is a human IgG1 $\gamma$  antibody that binds to soluble (but not transmembrane) B-lymphocyte stimulator (BLyS; also known as BAFF), a key survival factor for B lymphocytes. In 2 randomized, double-blind, placebo controlled trials, BLISS-52 and BLISS-76 (with numbers representing the duration of each trial in weeks), there was a small but statistically significant benefit in the primary outcome, the SLE Responder index (SRI) at 52 weeks in the 10 mg/kg treatment arm. In BLISS-76, this significance was lost during the blinded extension to 76 weeks. The SRI is a composite score of the following components:  $\geq 4$  point reduction in SELENA-SLEDAI score compared to baseline, no worsening in physician global assessment score, and no new BILAG A organ domain scores (organ involvement requiring immunosuppressive therapy) or  $>1$  new BILAG B organ domain scores (organ involvement requiring symptomatic therapy) at time of assessment. The SRI was identified on retrospective analysis of phase II studies as a combination of outcomes able to show benefit of belimumab treatment.

Patients had to meet all three of these components to be considered an SRI responder. Other secondary outcomes favoring belimumab over placebo were reduction in risk of severe flare, reduced steroid use, and improvements in health-related quality of life. An uncontrolled, open-label extension of the phase II trial showed sustained improvement in disease activity over five years.

### **Clinical Trial Response Rates at 52 and 76 weeks.**

<b>Trial</b>	<b>Placebo</b>	<b>Belimumab 1 mg/kg</b>	<b>Belimumab 10 mg/kg</b>
BLISS-52 at 52 weeks	N = 287	N = 288	N=290
SRI response rate	125 (44%)	148 (51%) P=0.013	167 (58%) P=0.001
BLISS-76 at 52 weeks	N = 275	N = 271	N = 273
SRI response rate	93 (34%)	110 (41%) NS	118 (43%) P=0.021
BLISS-76 at 76 weeks	N = 275	N = 271	N = 273
SRI response rate	89 (32%)	106 (39%) NS	105 (39%) NS

Enrollment in both phase III trials was limited to patients with a positive ANA or dsDNA. The most commonly involved organ systems at enrollment were musculoskeletal, mucocutaneous, and hematologic; improvement in the trials was largely due to effects on these organ systems. Belimumab has not been studied in patients with severe active lupus nephritis or severe active central nervous system disease. Subgroup analysis of SRI responses in African Americans and patients of African heritage (N=148), populations prone to SLE with greater severity, was less than that in the placebo group, but the numbers were too small to draw definitive conclusions.

### **Safety of Belimumab:**

Safety data from the long-term treatment extension demonstrated that the rates of adverse events, serious adverse events, serious infections, and malignancies in belimumab treated patients were equal to or lower than the rates during the placebo-controlled trials. Key safety findings included:

- Belimumab treatment was not associated with an increased risk of serious infections.
- Two opportunistic infections (disseminated cytomegalovirus [CMV] and acinetobacter bacteremia) were seen in the Belimumab 10 mg/kg group during the controlled trials. Six additional opportunistic infections were reported during long-term therapy (CMV pneumonia, mycobacterial infections and coccidiomycosis).
- The malignancy rate was comparable between placebo and belimumab treatment groups and consistent with the background rate reported for patients with SLE. No pattern of malignancy or an increase in any particular type of malignancy was identified in patients receiving belimumab.
- Mortality was similar for belimumab treatment versus placebo (0.55 per 100 patient-years vs. 0.43). The most common causes of death were infection, followed by cardiovascular disease.
- Depression was the most common psychiatric adverse event and was numerically more common with belimumab treatment than with placebo. There were 2 completed suicides in belimumab treated patients versus none in the placebo groups in the controlled trials.
- Hypersensitivity reactions and infusion reactions occurred in 17% of patients with belimumab treatment vs. 15% with placebo. These were generally mild. Serious hypersensitivity reactions occurred in 5 patients receiving belimumab.

#### **Supply, Administration and cost:**

Belimumab is approved at a dosage of 10 mg/kg to be given by intravenous infusions at 2-week intervals for the first 3 doses and 4-week intervals thereafter. Human Genome Sciences, the manufacturer, has announced that the drug will be priced at \$1,477.26 for a 400 mg. vial; this would result in an average price for the drug itself for one year of therapy of approximately \$35,000.

#### **The Bottom Line:**

Belimumab is the first new medication approved by the USA FDA for SLE in over 50 years. The patients most appropriate for therapy may be seropositive SLE patients with active musculoskeletal, cutaneous, and immunological activity despite standard of care. Belimumab has not been studied in severe active lupus nephritis or severe active CNS lupus.

Belimumab was not associated with an increase in serious adverse events, infections or malignancy during clinical trials. Severe hypersensitivity reactions, though rare, were reported in belimumab treated patients. Longer term followup of larger numbers of diverse SLE patients is needed to better assess this agent's safety.

1. **FDA Briefing Information, Belimumab (BENLYSTA), for the November 16, 2010 Meeting of the Arthritis Advisory Committee.**
2. Jacobi AM, *et al*: **Effect of long-term belimumab treatment on B cells in systemic lupus erythematosus: extension of a phase II, double-blind, placebo-controlled, dose-ranging study.** *Arthritis Rheum* 2010, **62**(1):201-210.
3. Navarra SV, *et al*: **Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial.** *Lancet* 2011, **377**(9767):721-731.
4. Wallace DJ, *et al*: **A phase II, randomized, double-blind, placebo-controlled, dose-ranging study of belimumab in patients with active systemic lupus erythematosus.** *Arthritis Rheum* 2009, **61**(9):1168-1178.

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