Published in final edited form as:
Arthritis Rheum. 2009 September 15; 61(9): 1168–1178. doi:10.1002/art.24699.

A Phase II, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study of Belimumab in Patients With Active Systemic Lupus Erythematosus

Daniel J. Wallace, MD, FACP, FACR,
Cedars-Sinai Medical Center, UCLA, Los Angeles, California

William Stohl, MD, PhD,
University of Southern California Keck School of Medicine and Los Angeles County + University of Southern California Medical Center, Los Angeles, California

Richard A. Furie, MD,
North Shore-Long Island Jewish Health System, Lake Success, New York

Jeffrey R. Lisse, MD,
The University of Arizona Arthritis Center, Tucson, Arizona

James D. McKay, DO,
Oklahoma Center for Arthritis Therapy and Research, Tulsa, Oklahoma

Joan T. Merrill, MD,
Oklahoma Medical Research Center, Oklahoma City, Oklahoma

Michelle A. Petri, MD, MPH,
Johns Hopkins University, Baltimore, Maryland

Ellen M. Ginzler, MD, MPH,
SUNY Downstate Medical Center, Brooklyn, New York

W. Winn Chatham, MD,
University of Alabama at Birmingham, Birmingham, Alabama

W. Joseph McCune, MD,
University of Michigan Medical Center, Ann Arbor, Michigan

Vivian Fernandez,
Human Genome Sciences Inc, Rockville, Maryland

Marc R. Chevrier, MD, PhD, FACR,
Human Genome Sciences Inc, Rockville, Maryland

John Zhong, PhD, and
Human Genome Sciences Inc, Rockville, Maryland

William W. Freimuth, MD, PhD
Human Genome Sciences Inc, Rockville, Maryland

Abstract

Address correspondence and reprint requests to Daniel J. Wallace, MD, 8737 Beverly Blvd Suite 302 West Hollywood, CA 90048, USA. Tel: (310) 652-0920, Fax: (310) 360-4812, dwallace@ucla.edu.
currently at Centocor, Inc, Horsham, Pennsylvania

Objective—To assess the safety, tolerability, biological activity, and efficacy of belimumab in combination with standard of care therapy (SOC) in patients with active systemic lupus erythematosus (SLE).

Methods—Patients with SELENA-SLEDAI score≥4 (N=449) were randomly assigned to belimumab (1, 4, 10 mg/kg) or placebo in a 52-week study. Co-primary endpoints were: 1) percentage change in the SELENA-SLEDAI score at week 24; 2) time to the first SLE flare.

Results—Significant differences between the treatment and placebo groups were not attained for either primary endpoint and no dose response was observed. Reduction in SELENA-SLEDAI score from baseline was 19.5% in the combined belimumab group versus 17.2% in the placebo group. The median time to first SLE flare was 67 days in the combined belimumab group versus 83 days in the placebo group. However, the median time to first SLE flare during weeks 24–52 was significantly longer with belimumab treatment (154 versus 108 days; P=0.0361). In the subgroup (71.5%) of serologically active patients (ANA ≥1:80 and/or anti-dsDNA ≥30 IU/mL), belimumab treatment resulted in significantly better responses at week 52 than placebo for SELENA-SLEDAI (−28.8% versus −14.2%; P=0.0435); PGA (−32.7% versus −10.7%; P=0.0011); and SF-36 PCS (+3.0 versus +1.2 points; P=0.0410). Treatment with belimumab resulted in 63–71% depletion of naive, activated, and plasmacytoid $CD20^+$ B cells and a 29.4% reduction in anti-dsDNA titers ($P \leq 0.0017$) by week 52. The rates of adverse events (AEs) and serious AEs were similar in the belimumab and placebo groups.

Conclusion—Belimumab was biologically active and well tolerated. Belimumab effect on the reduction of SLE disease activity or flares was not significant. However, serologically active SLE patients responded significantly better to belimumab therapy plus SOC than SOC alone.

INTRODUCTION

B-lymphocyte stimulator (BLyS), a 285–amino acid protein member of the tumor necrosis factor (TNF) ligand superfamily, is a key B-cell survival factor (1) and binds 3 membrane receptors (TACI, BCMA, BAFF-R/BR3) on B lymphocytes (2–4). BLyS inhibits B-cell apoptosis and stimulates the differentiation of B cells into immunoglobulin-producing plasma cells (5). Constitutive overexpression of BLyS by mice that harbor a *blys* transgene results in a systemic lupus erythematosus (SLE)-like autoimmune-like disease (6–8). Conversely, genetic disruption of the *blys* gene in SLE-prone NZM 2328 mice markedly attenuates development of clinical disease (9). Moreover, soluble BLyS receptors (TACI-Fc or BR3-Fc) administered to SLE prone (NZBxNZW) F1 or MRL-*lpr/lpr* mice slowed disease progression and improved survival (2,10).

BLyS is overexpressed in patients with SLE and other autoimmune diseases (11–14). BLyS levels and mRNA expression correlate with changes in SLE disease activity and anti-dsDNA antibody titers (11,14–16).

Belimumab (LymphoStat B; Human Genome Sciences) is a fully human IgG1-λ monoclonal antibody that binds to soluble human BLyS and inhibits its biological activity (17,18). In a phase I dose-escalation study performed in 70 SLE patients, no related serious adverse events (AEs) or safety signals were reported, and evidence of biological activity included reductions in $CD20^+$ B cells and anti-dsDNA antibody titers (19). A phase II dose-ranging trial of belimumab was designed to evaluate the safety, efficacy, and biological activity of belimumab in SLE patients with active disease who were receiving standard of care therapy (SOC). Secondary and exploratory analyses were performed to better understand belimumab's effects and to identify the ideal study population for phase III studies.

PATIENTS AND METHODS

Study Design

Patients were randomized to receive 1, 4, or 10 mg/kg of belimumab or placebo by intravenous infusion over 2 hours on days 0, 14, 28, and then every 28 days for 52 weeks plus SOC. Hematology, chemistry, urinalysis, 24-hour urine collection, biological markers, autoantibodies, SLE disease activity scales (Safety of Estrogen in Lupus Erythematosus National Assessment SLE Disease Activity Index [SELENA-SLEDAI] (20), SELENA-SLEDAI Flare Index [SFI] (21), and the British Isles Lupus Assessment Group [BILAG] instrument [22,23]), Physician's Global Assessment (PGA), and SF-36 Health Survey (SF-36) (24) were evaluated every 4 weeks during the first 24 weeks, and then at weeks 32, 40, 48, and 52. Changes to immunosuppressive agents and corticosteroid therapy were permitted as clinically indicated.

Entry criteria

Adult (≥ 18 years) patients fulfilling the American College of Rheumatology (ACR) criteria for SLE who had active disease as defined by a SELENA-SLEDAI score ≥4 at screening were eligible for enrollment (25). Inclusion criteria mandated a history of measurable autoantibodies (including any of the following: antinuclear antibodies [ANA], anti-dsDNA, anti-Smith, anti-RNP, anti-Ro, anti-La, or anti-cardiolipin), but they did not have to be present at screening. In addition, adult patients were required to be on a stable regimen of prednisone (5–40 mg/day), antimalarials, or immunosuppressives for at least 60 days prior to day 0 (first dose). Key exclusion criteria included active lupus nephritis or central nervous system disease, pregnancy, and receipt of cyclosporine, intravenous immunoglobulin (Ig), biologics, cyclophosphamide, or doses of prednisone >100 mg/day within 6 months. Patients were stratified according to their screening SELENA-SLEDAI scores (4–7 versus ≥8).

Efficacy measures

The co-primary efficacy endpoints were the percent change in SELENA-SLEDAI score from baseline (day 0) to week 24 and time to first mild/moderate or severe flare as defined by the SFI (21) during 52 weeks. Secondary efficacy endpoints included changes in week 52 SELENA-SLEDAI and BILAG scores, time to first SLE flare (assessed by SFI or BILAG) during and after the first 24 weeks, and the percentage of patients with a prednisone dose ≤7.5 mg/day or reduced by 50% from baseline during weeks 40–52. Other secondary efficacy endpoints evaluating change from baseline over 52 weeks included autoantibody and complement levels, corticosteroid doses, B-cell and plasma cell subsets, PGA, SF-36, impact on organ-specific disease, and Ig levels. Exploratory analyses were performed to identify subgroups with superior treatment responses.

Biological markers, autoantibodies, and B-cell populations

Anti-dsDNA antibody, ANA, IgG, IgM, IgE, IgA, and complement (C3 and C4) levels were measured every 1 to 2 months. Serum BLyS levels were determined only at day 0 (prior to belimumab dosing) because belimumab interferes with accurate measurements of BLyS (26). Antinuclear antibodies were determined by a screening enzyme-linked immunosorbent assay (ELISA), and all positive samples underwent immunofluorescence testing on HEp-2 cells (Quest Laboratories, Van Nuys, CA). Peripheral blood lymphocytes, collected every 1 to 2 months, were forwarded to a central fluorescence-activated cell sorting (FACS) facility (Nichols Laboratory, La Jolla, CA). Cells were stained with combinations of antibodies to identify multiple B cell subsets (naive [$CD20^+/CD27^-$], memory [$CD20^+/CD27^+$], activated [$CD20^+/CD69^+$], plasmacytoid [$CD20^+/CD138^+$]) and plasma cells ($CD20^-/CD138^+$ and

$CD20^{-}/CD27^{HI}$), as well as a specific SLE subset ($CD19^{+}/CD38^{BRIGHT}/CD27^{BRIGHT}$) of plasma cells (27).

Statistical methods

Differences in SELENA-SLEDAI scores at week 24 between groups were analyzed using a 2-sample *t* test, and the time to first flare over 52 weeks was evaluated with the log-rank test. Missing data in SELENA-SLEDAI were imputed using a last observation carried forward (LOCF) method. The analysis of primary efficacy endpoints was performed in a modified intention-to-treat (mITT) population, defined as all patients who were randomized and received a dose of study agent. Discrete variables were analyzed using a likelihood chi-squared test and continuous variables using the Student *t* test or the Wilcoxon rank sum test, as appropriate.

The sample size was based on the 2 co-primary efficacy endpoints. The study was designed to have at least 80% power at a 2.5% significance level to detect in one of the active groups: 1) a 25% absolute or 100% relative improvement in the percent change from baseline score in SELENA-SLEDAI (assuming an average decrease of 25% from baseline in the placebo group with a SD of 50%) at week 24, and 2) a reduction in the percent of patients having their first SLE flare by week 52 from 65% in the placebo group to 43% in any one of the belimumab treatment groups.

Informed consent

All patients gave written informed consent, which was approved by either a central or local Institutional Review Board. An independent Data Monitoring Committee reviewed safety data approximately every 3 months.

RESULTS

Patient Disposition and Demographics

Belimumab was administered to 336 patients and placebo to 113 patients at 59 sites in the United States and Canada from October 2003 to August 2005 (Figure 1). There were no significant differences among treatment groups in baseline features (Table 1) or in reasons for discontinuation (Figure 1).

Efficacy

Primary clinical endpoints

Changes in SELENA-SLEDAI scores: There were no significant differences between any of the individual belimumab treatment groups and the placebo group with regard to the percent changes in SELENA-SLEDAI scores from baseline to weeks 24 or 52. Mean percent changes in SELENA-SLEDAI were −19.5% for combined belimumab groups versus −17.2% for the placebo group at 24 weeks, and −27.2% for the all-belimumab-treated group versus −20.6% for the placebo group at 52 weeks (Table 2). Dose-dependent effects on changes in SELENA-SLEDAI score were not observed. The modification of the SELENA-SLEDAI score by excluding contributions of anti-dsDNA and/or low complement did not reduce the treatment effect of belimumab (Table 2).

Flare rates: Based on the SFI, 59%, 78%, and 87% of all patients (including placebo) experienced a flare (mild-moderate or severe) by weeks 12, 24, and 52, respectively, and there were no differences among the four treatment groups dose dependent (Figure 2A). Severe flares were reported in 32% of both belimumab and placebo groups over 52 weeks. Excluding severe flares triggered solely by SELENA-SLEDAI score changes to >12 without

clinical manifestations, the severe flare rate was 20.4% in the placebo group and 15.2% in the belimumab group (*P*=0.2080).

Time to first flare: There was no significant difference in time to first SFI-defined flare over 52 weeks between the combined belimumab and placebo groups (67 versus 83 days, respectively) (Table 2). However, an analysis of time to first flare starting at week 24 through week 52 (Figure 2B and Table 2) revealed a median time to flare of 154 days in the belimumab group and 108 days in the placebo group (*P*=0.0361), suggesting that belimumab can stabilize disease, but requires some time to do so. During the second half of the study (weeks 24–52), severe flares were observed in 12% of belimumab-treated and in 17% of placebo-treated patients (*P*=0.1807).

Secondary and exploratory clinical endpoints in all patients

Corticosteroid dose and immunosuppressive drugs: Among patients whose baseline prednisone dose was >7.5 mg/day, 44.7% of patients receiving 10 mg/kg of belimumab were able to reduce their steroid dose by 50% or to ≤7.5 mg/day in the last 3 months prior to the week 52 visit (versus 27.1% in the placebo group; *P*=0.0882). The prednisone dose during the last 2 months of the study was reduced an average of 3.1 mg/day (−19.9%) in the combined belimumab group versus 1.9 mg/day (−11.7%) in the placebo group with the 10-mg/kg treatment group having the best response (6.4 mg/day; −40.5%; *P*=0.2218). In patients on either no steroids or low-dose steroids (≤7.5 mg/day) at baseline, 2.7% of 10 mg/kg belimumab-treated patients (compared with 12.3% of placebo patients) (*P*=0.0459) (Table 2) had their average prednisone dose increased to >7.5 mg/day. Over 52 weeks of therapy, a new immunosuppressive agent was added to 6.2% of patients in the combined belimumab group versus 11.5% of the placebo group (P=0.0799) and no significant differences were observed in discontinuing an immunosuppressive agent.

Physician's Global Assessment and SF-36 Physical Component Score (PCS): Significant mean changes in PGA (21) in the combined belimumab group were observed as early as week 4, and by 52 weeks there was a 31% decrease in mean PGA score in the combined belimumab group compared with a 14% decrease in the placebo group (*P*=0.0019) (Table 2). Similarly, there was a trend toward improvement in the PCS of the SF-36 (24) at week 52 in the combined belimumab group (+2.6 points versus +1.4 points in the placebo group; *P*=0.0979). Significant increases of 3.4 points in the PCS at week 52 in patients receiving 10 mg/kg dose of belimumab were observed (*P*=0.0167) (Table 2). An increase from baseline of ≥2.5 points in the PCS is considered to be the minimal clinically important difference (MCID) (28).

BILAG: The incidence of new A or B organ system domain flares in the combined belimumab group was similar to those in the placebo group at week 52 (29.5% versus 35.4%; *P*=0.2416) (Table 2). Moreover, there were no significant improvements in mean BILAG composite scores or individual organ domain scores in belimumab-treated groups compared with placebo (results not shown).

Exploratory subgroup analyses of SELENA-SLEDAI responses (Figure 2C): Statistically significant percent changes in SELENA-SLEDAI scores from baseline to week 52 were associated with belimumab treatment compared with placebo treatment in patients with the following baseline characteristics: anti-dsDNA antibody positivity, low C3, low C4, prednisone dose >7.5 mg/day, and serological activity (ANA ≥1:80 or anti-dsDNA antibody >30 IU/mL) at both screening and day 0. Baseline characteristics associated with favorable trends in SELENA-SLEDAI scores (mean difference between belimumab treatment and

placebo ≥10% reduction but not statistically significant) were SELENA-SLEDAI≥8, ANA ≥1:80 at both screening and day 0, and elevated BLyS levels at day 0.

Biological activity

B-cell subsets: There was no significant dose response observed in modulation of B-cell subsets (Figure 3), plasma cell subsets (data not shown), or with any of the other biomarkers examined (C3, C4, anti-dsDNA antibody, ANA, or Ig isotypes) in the belimumab groups over 52 weeks (data not shown). Therefore, all belimumab treatment groups were combined for analyses of biomarker data. Continuous treatment with belimumab led to significant median percent reductions by week 24 of 30–59% ($P<0.0001$) in selected B-cell counts/mm^3, and by week 52, the percent changes were: $CD19^+$, −49.3%; $CD20^+$, −54.1%; naive B-cells, −70.8%; activated B-cells, −70.4%; plasmacytoid B cells, −62.5%. Conversely, in the combined belimumab group, the percent change in the median value of memory B-cells was increased 88% by day 28 ($P<0.0001$) and gradually returned to baseline by week 52 (Figure 3D). The percent changes from baseline in the SLE subset of plasma cells at week 52 were significantly different in the belimumab treatment group (−18.2%) from the placebo group (+28.6%; $P=0.0027$). No significant group differences were noted in the changes in plasma cells between belimumab and placebo groups.

Immunoglobulin concentrations: Median serum concentrations of IgG, IgA, IgM, and IgE decreased by 10%, 14%, 29%, and 34%, respectively, at week 52 in the belimumab-treated group ($P<0.0001$ for all Ig isotypes) compared with a <5% change from baseline for the placebo group (data not shown). Reductions were observed as early as week 8 in all Ig isotypes. There was a significantly greater number of patients on belimumab (31.4% versus 19.4% placebo; $P<0.0192$) who had low IgM at week 52, but not IgG or IgA (Table 3).

Antinuclear antibodies and complement: IgG anti-dsDNA antibodies decreased early in the study. In patients with IgG anti-dsDNA antibodies at baseline, median reductions of 29.4% and 8.6% were observed in the combined belimumab and placebo groups, respectively ($P=0.0017$). Anti-dsDNA antibodies became negative in 14.6% of belimumab-treated patients versus 3.4% of placebo patients at week 52 ($P=0.0119$). Median changes in C4 in the belimumab group at week 52 were: +22.7% versus +7.7% in the placebo group ($P<0.0001$) for all treated patients and +33.3% versus +14.3% in the placebo group ($P=0.0143$) in those patients with low (<16 mg/dL) baseline C4 concentrations (data not shown). Median percent changes in C3 at week 52 were −2.1% in belimumab-treated patients versus −6.5% in the placebo group ($P=0.0362$) and +6.3% in patients with low (<90 mg/dL) C3 at baseline versus −0.8% in the placebo group ($P=0.15$).

Safety and tolerability

During the 52-week study and 8-week follow-up period, the incidence of AEs by individual event or Medical Dictionary for Regulatory Activities (MedDRA) system organ class, serious or severe AEs, and laboratory abnormalities were similar in all treatment groups, including placebo (Table 3). Only urticaria was statistically more frequent in belimumab-treated patients (4% versus 0%). No significant dose-related increase in AEs was observed. Serious AEs occurred in 19.5% of placebo patients compared with 16.1% of patients in all belimumab-treated groups. The incidence of infections was 72.6% in the placebo group versus 75.6% in the belimumab groups (Table 3). Serious infections occurred in 5.1% of belimumab-treated patients compared with 3.5% in the placebo group. Although pneumonia and cellulitis were the most common serious infections, no specific type of infection was more prominent in any of the groups (Table 3). Two deaths (1 suicide and 1 respiratory failure in the 1 mg/kg and 10 mg/kg groups, respectively) were reported, and neither were considered to be related to the study drug by the investigator. A basal cell carcinoma in a

patient given placebo (0.9%) and a squamous cell carcinoma in a patient on 10 mg/kg of belimumab (0.3%) were reported. One “severe” infusion reaction, consisting of pruritus, occurred in a belimumab-treated patient and resulted in discontinuation of the study drug.

Exploratory subgroup analyses in serologically active patients at baseline

The 321 serologically active patients were compared with 128 patients who were seronegative (29). At study entry, patients in the serologically active group were more often African-American (27% versus 16%; P=0.0199), fulfilled a greater number of ACR SLE criteria (P<0.01), were younger (41 versus 46 years; P<0.0001), had more major organs involved (eg, renal 34% versus 19%; hematologic 59% versus 33%), fewer cutaneous manifestations, higher mean SELENA-SLEDAI scores (9.8 versus 8.9), greater prednisone use (72.6% versus 57.8%; P =0.0027), lower C3 and C4 levels (P<0.0001), higher Ig levels (IgG, IgA, and IgE; all P≤0.001), lower baseline $CD19^+$ and $CD20^+$ B-cell counts (P≤0.01), and more often detectable (≥0.350 ng/mL) BLyS levels (51% versus 24%; P<0.0001) (29).

Serologically active patients treated with belimumab had significantly greater reductions in SELENA-SLEDAI scores from baseline to week 52 (−28.8% in the combined belimumab group versus −14.2% in the placebo group; P=0.0435) and using a modified SELENA-SLEDAI scoring excluding contributions of anti-dsDNA and low complement (Table 2). In addition, belimumab treatment resulted in improvements in both the PGA (−32.7% in the combined belimumab group versus −10.7% in the placebo group; P=0.0011) and SF-36 PCS (3.0-point increase in the combined belimumab group versus 1.2-point increase in the placebo group; P=0.041). There was no significant effect seen in BILAG composite score (data not shown). However, there were fewer new BILAG A or B flares in the combined belimumab group (29.4%, versus 39.5% in the placebo group; P=0.0871) (Table 2). Analysis of treatment effects on PGA revealed that 63.8% of belimumab-treated versus 46.5% of placebo-treated serologically active patients (P=0.0054) had a >0.3-point improvement in PGA.

Overall, there were no statistically significant differences in biomarker responses between serologically active and all patients (data not shown) or between serologically active and inactive patients (data not shown). In addition, in serologically active patients, there were no significant differences across belimumab dosing groups or between treatment and placebo groups in safety profile (data not shown).

DISCUSSION

In this phase II study, belimumab treatment combined with SOC therapy in SLE patients with active disease did not result in significant improvement compared with placebo as assessed by the co-primary endpoints of SELENA-SLEDAI score reduction at week 24 or reduction in time to first SLE flare over 52 weeks. Nevertheless, this trial provided evidence that belimumab was well tolerated and improved many secondary disease activity measures (SLE flares, PGA, SELENA-SLEDAI, SF-36 PCS) when added to SOC in a large (71.5%) subpopulation of serologically active patients. It generated a clinically meaningful hypothesis that provides the basis for the design of phase III confirmatory studies. The phase II study provided 4 valuable insights into the pharmacodynamics of belimumab, SLE disease activity, and trial design.

First, significant early reductions in selected B cells initially observed 4 to 8 weeks after belimumab treatment and early improvement in PGA observed at 4 weeks after belimumab treatment appear to require time to translate into clinically important benefit as measured by SELENA-SLEDAI or SFI. Support for this assertion lies in the analysis of time to first SLE

flare after 24 weeks, which showed significant lengthening from 108 days in the placebo group to 154 days in the belimumab groups.

Second, the presumption of an annual flare rate of 65% to 70% was too low. Eighty-seven percent of patients in this study had a mild-moderate or severe flare by week 52, which was greater than the annual frequency (65%) reported by the SELENA-SLEDAI group (21) employing the same flare instrument. Using new BILAG A or B domain scores as a definition of flare (30), it was observed that 69% of patients had a flare in 1 year. Additionally, in 3 trials evaluating the effects of oral contraceptives (OC) (20), contraceptive methods (CM) (31), or hormone replacement therapy (HRT) (32) on SLE disease activity, the 1-year SFI flare rates were 76% (OC), 69% (OC placebo), 67% (CM-OC), 74% (CM-progestin or IUD), 64% (HRT), and 51% (HRT placebo). The high early flare rate in our study made it difficult to detect an effect, and was probably related to greater disease activity (baseline SELENA-SLEDAI score 9.6) in our study population compared with those reported in recent long-term studies in which baseline SELENA-SLEDAI scores were 3.2 (20), 5.8 (31), 2.5 (32), and 3.3 (16).

Third, permitting unlimited changes in prednisone and immunosuppressive medications during the trial could have confounded SLE disease activity assessments. Additional therapy, especially when given within 8 weeks of week 52, could have affected study endpoints. Prednisone use was lower in the belimumab groups, as evidenced by greater percentages of patients having reduced prednisone by ≥50% or to <7.5 mg/day and fewer patients required an increase to >7.5 mg/day than in the placebo group. Less prednisone use among belimumab-treated patients could have blunted the detection of a difference from placebo-treated groups.

Fourth, serologically active patients were far more appropriate for belimumab B-cell–targeted therapy than seronegative patients. Although 98% of patients had verified reports of previously positive ANA tests or other SLE autoantibodies, only 71.3% of patients had an ANA ≥1:80 at baseline, and 50% were anti-dsDNA antibody positive. Although some of this discrepancy could be attributed to a lack of uniformity between autoantibody testing laboratories, the finding that significant improvement in SELENA-SLEDAI score at week 52 with belimumab was associated with serologically active patients at screening and baseline strongly suggests that this was a more clinically active population. BLyS levels above the limit of quantitation at baseline were detected in twice as many serologically active (51%) as seronegative (24%) patients. Serologically active patients were significantly more responsive to belimumab, particularly in PGA and SF-36 PCS responses. Thus, a subset of seronegative patients making up 28% of the original cohort could have confounded the assessment of belimumab efficacy.

Depletion (63%–71%) of $CD20^+$ subsets of naive, activated, and plasmacytoid B cells after 1 year of treatment confirmed that belimumab was biologically active and also supports the role of BLyS as an essential B-cell growth and survival factor. A more rapid reduction of B-cell subsets occurred in the first 6 months than in the second 6 months. Peripheral memory B cells doubled in number after 1 month of belimumab treatment, but returned to baseline levels by 1 year. The initial increase of memory B cells may be secondary to a release from disrupted lymphoid germinal centers, as seen in cynomolgus monkeys (18), or caused by inhibition of memory B-cell return to germinal centers (33), or promotion of differentiation of naive B cells to memory B cells. Peripheral blood plasma cells were not reduced following a year of belimumab therapy. Patients on belimumab had decreases in a plasma cell subset that has been correlated with SLE activity (27), whereas there was an increase in placebo patients. Plasma cell survival has been shown to be more dependent on BCMA expression because there is less BAFF-R/BR3 expression on plasma cells than on $CD20^+$ B

cells (34–36), and plasmablasts appear more dependent on A Proliferation-Inducing Ligand (APRIL) for bone marrow survival (37). One year of belimumab therapy led to a 29% reduction in IgG anti-dsDNA antibody compared with a 10% reduction in IgG, suggesting a selective effect on autoantibody-producing cells thought to be short-lived plasmablasts or plasmacytoid B cells (27,38).

Belimumab in combination with SOC was well tolerated. The incidence of AEs, serious or severe AEs, reasons for discontinuation, and laboratory abnormalities were similar across the 3 doses of belimumab and the placebo group. There was no dose relationship for infection rates or serious infections for patients receiving belimumab, and no specific type of infection was prominent in any of the 4 treatment groups. The preservation of long-lived plasma cells and memory B cells, and only a modest reduction in IgG likely contributed to the similar infection rates in the belimumab and placebo groups. In murine SLE, animals given anti-BLyS antibody therapy had similar alterations in B cells, and there were no significant effects on primary and secondary immune responses (35).

In summary, developing new therapies for a heterogeneous disease such as SLE remains challenging (39). Use of the SELENA-SLEDAI and BILAG disease activity scales in this large randomized, controlled trial identified limitations and strengths of these tools, and suggested that using the same scales to show improvement and worsening could be problematic. Therefore, to demonstrate the effectiveness of belimumab while complying with regulatory requirements and with the Food and Drug Administration (FDA) draft guidance document on the development of therapies for SLE, a novel combined endpoint based upon the data from this phase II study was developed (40). The results of this trial provided valuable information with which to design 2 large phase III SLE studies evaluating the effects of 2 doses of belimumab in serologically active SLE patients.

Acknowledgments

Supported in part by NIH grant M01 RR00043 to the General Clinical Research Center at the University of Southern California Keck School of Medicine, Los Angeles, California.

References

1. Moore PA, Belvedere O, Orr A, Pieri K, LaFleur DW, Feng P, et al. BLyS: member of the tumor necrosis factor family and B lymphocyte stimulator. Science. 1999; 285(5425):260–3. [PubMed: 10398604]
2. Gross JA, Johnston J, Mudri S, Enselman R, Dillon SR, Madden K, et al. TACI and BCMA are receptors for a TNF homologue implicated in B-cell autoimmune disease. Nature. 2000; 404(6781): 995–9. [PubMed: 10801128]
3. Xia XZ, Treanor J, Senaldi G, Khare SD, Boone T, Kelley M, et al. TACI is a TRAF-interacting receptor for TALL-1, a tumor necrosis factor family member involved in B cell regulation. J Exp Med. 2000; 192(1):137–43. [PubMed: 10880535]
4. Yan M, Brady JR, Chan B, Lee WP, Hsu B, Harless S, et al. Identification of a novel receptor for B lymphocyte stimulator that is mutated in a mouse strain with severe B cell deficiency. Curr Biol. 2001; 11(19):1547–52. [PubMed: 11591325]
5. Do RK, Hatada E, Lee H, Tourigny MR, Hilbert D, Chen-Kiang S. Attenuation of apoptosis underlies B lymphocyte stimulator enhancement of humoral immune response. J Exp Med. 2000; 192(7):953–64. [PubMed: 11015437]
6. Gross JA, Dillon SR, Mudri S, Johnston J, Littau A, Roque R, et al. TACI-Ig neutralizes molecules critical for B cell development and autoimmune disease. impaired B cell maturation in mice lacking BLyS. Immunity. 2001; 15(2):289–302. [PubMed: 11520463]
7. Khare SD, Sarosi I, Xia XZ, McCabe S, Miner K, Solovyev I, et al. Severe B cell hyperplasia and autoimmune disease in TALL-1 transgenic mice. PNAS. 2000; 97(7):3370–5. [PubMed: 10716715]

8. Mackay F, Woodcock SA, Lawton P, Ambrose C, Baetscher M, Schneider P, et al. Mice transgenic for BAFF develop lymphocytic disorders along with autoimmune manifestations. J Exp Med. 1999; 190(11):1697–710. [PubMed: 10587360]
9. Jacob CO, Pricop L, Putterman C, Koss MN, Liu Y, Kollaros M, et al. Paucity of clinical disease despite serological autoimmunity and kidney pathology in lupus-prone New Zealand mixed 2328 mice deficient in BAFF. J Immunol. 2006; 177(4):2671–80. [PubMed: 16888029]
10. Kayagaki N, Yan M, Seshasayee D, Wang H, Lee W, French DM, et al. BAFF/BLyS receptor 3 binds the b cell survival factor BAFF ligand through a discrete surface loop and promotes processing of NF-kB2. Immunity. 2002; 17:515–24. [PubMed: 12387744]
11. Cheema GS, Roschke V, Hilbert DM, Stohl W. Elevated serum B lymphocyte stimulator levels in patients with systemic immune-based rheumatic diseases. Arthritis Rheum. 2001; 44(6):1313–9. [PubMed: 11407690]
12. Groom J, Kalled SL, Cutler AH, Olson C, Woodcock SA, Schneider P, et al. Association of BAFF/BLyS overexpression and altered B cell differentiation with Sjogren's syndrome. J Clin Invest. 2002; 109(1):59–68. [PubMed: 11781351]
13. Mariette X, Roux S, Zhang J, Bengoufa D, Lavie F, Zhou T, et al. The level of BLyS (BAFF) correlates with the titre of autoantibodies in human Sjogren's syndrome. Ann Rheum Dis. 2003; 62(2):168–71. [PubMed: 12525388]
14. Zhang J, Roschke V, Baker KP, Wang Z, Alarcon GS, Fessler BJ, et al. Cutting edge: a role for B lymphocyte stimulator in systemic lupus erythematosus. J Immunol. 2001; 166(1):6–10. [PubMed: 11123269]
15. Collins CE, Gavin AL, Migone TS, Hilbert DM, Nemazee D, Stohl W. B lymphocyte stimulator (BLyS) isoforms in systemic lupus erythematosus: disease activity correlates better with blood leukocyte BLyS mRNA levels than with plasma BLyS protein levels. Arthritis Res Ther. 2006; 8(1):R6. [PubMed: 16356193]
16. Petri M, Stohl W, Chatham W, McCune WJ, Chevrier M, Ryel J, et al. Association of plasma B-Lymphocyte stimulator (BLyS) levels and disease activity in systemic lupus erythematosus. Arthritis Rheum. 2008; 58(8):2453–9. [PubMed: 18668552]
17. Baker KP, Edwards BM, Main SH, Choi GH, Wager RE, Halpern WG, et al. Generation and characterization of LymphoStat-B, a human monoclonal antibody that antagonizes the bioactivities of B lymphocyte stimulator. Arthritis Rheum. 2003; 48(11):3253–65. [PubMed: 14613291]
18. Halpern WG, Lappin P, Zanardi T, Cai W, Corcoran M, Zhong J, et al. Chronic administration of belimumab, a BLyS antagonist, decreases tissue and peripheral blood B-lymphocyte populations in cynomolgus monkeys: pharmacokinetic, pharmacodynamic, and toxicologic effects. Toxicol Sci. 2006; 91(2):586–99. [PubMed: 16517838]
19. Furie R, Stohl W, Ginzler EM, Becker M, Mishra N, Chatham W, et al. Biologic activity and safety of belimumab, a neutralizing anti-B-lymphocyte stimulator (BLyS) monoclonal antibody: a phase I trial in patients with systemic lupus erythematosus. Arthritis Res Ther. 2008; 10(5):R109. [PubMed: 18786258]
20. Petri M, Kim MY, Kalunian KC, Grossman J, Hahn BH, Sammaritano LR, et al. Combined oral contraceptives in women with systemic lupus erythematosus. N Engl J Med. 2005; 353(24):2550–8. [PubMed: 16354891]
21. Petri M, Buyon J, Kim M. Classification and definition of major flares in SLE clinical trials. Lupus. 1999; 8(8):685–91. [PubMed: 10568907]
22. Hay EM, Bacon PA, Gordon C, Isenberg DA, Maddison P, Snaith ML, et al. The BILAG index: a reliable and valid instrument for measuring clinical disease activity in systemic lupus erythematosus. Q J Med. 1993; 86(7):447–58. [PubMed: 8210301]
23. Isenberg DA, Gordon C. From BILAG to BLIPS--disease activity assessment in lupus past, present and future. Lupus. 2000; 9(9):651–4. [PubMed: 11199918]
24. Ware JE Jr, Gandek B. Overview of the SF-36 Health Survey and the International Quality of Life Assessment (IQOLA) Project. J Clin Epidemiol. 1998; 51(11):903–12. [PubMed: 9817107]
25. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1997; 40(9):1725. [PubMed: 9324032]

26. Cambridge G, Leandro MJ, Teodorescu M, Manson J, Rahman A, Isenberg DA, et al. B cell depletion therapy in systemic lupus erythematosus: effect on autoantibody and antimicrobial antibody profiles. Arthritis Rheum. 2006; 54(11):3612–22. [PubMed: 17075806]
27. Jacobi AM, Odendahl M, Reiter K, Bruns A, Burmester GR, Radbruch A, et al. Correlation between circulating CD27high plasma cells and disease activity in patients with systemic lupus erythematosus. Arthritis Rheum. 2003; 48(5):1332–42. [PubMed: 12746906]
28. Strand V, Crawford B. Improvement in health-related quality of life in patients with SLE following sustained reductions in anti-dsDNA antibodies. Expert Review of Pharmacoeconomics and Outcomes Research. 2005; 5:317–26. [PubMed: 19807601]
29. Petri M, Wallace DJ, Stohl W, McKay J, Stern S, Furie R, et al. SLE patients with active production of anti-nuclear autoantibodies (ANA) have distinct patterns of lupus activity and peripheral B-cell biomarkers compared to ANA negative patients. Ann Rheum Dis. 2006; 65(Suppl_2):356.
30. Gordon C, Sutcliffe N, Skan J, Stoll T, Isenberg DA. Definition and treatment of lupus flares measured by the BILAG index. Rheumatology (Oxford). 2003; 42(11):1372–9. [PubMed: 12810926]
31. Sanchez-Guerrero J, Uribe AG, Jimenez-Santana L, Mestanza-Peralta M, Lara-Reyes P, Seuc AH, et al. A trial of contraceptive methods in women with systemic lupus erythematosus. N Engl J Med. 2005; 353(24):2539–49. [PubMed: 16354890]
32. Buyon JP, Petri MA, Kim MY, Kalunian KC, Grossman J, Hahn BH, et al. The effect of combined estrogen and progesterone hormone replacement therapy on disease activity in systemic lupus erythematosus: a randomized trial. Ann Intern Med. 2005; 142(12 Pt 1):953–62. [PubMed: 15968009]
33. Badr G, Borhis G, Lefevre EA, Chaoul N, Deshayes F, Dessirier V, et al. BAFF enhances chemotaxis of primary human B cells: a particular synergy between BAFF and CXCL13 on memory B cells. Blood. 2008; 111(5):2744–54. [PubMed: 18172003]
34. O'Connor BP, Raman VS, Erickson LD, Cook WJ, Weaver LK, Ahonen C, et al. BCMA is essential for the survival of long-lived bone marrow plasma cells. J Exp Med. 2004; 199(1):91–8. [PubMed: 14707116]
35. Scholz JL, Crowley JE, Tomayko MM, Steinel N, O'Neill PJ, Quinn WJ III, et al. BLyS inhibition eliminates primary B cells but leaves natural and acquired humoral immunity intact. Proc Natl Acad Sci. 2008; 105(40):15517–22. [PubMed: 18832171]
36. Zhang X, Park CS, Yoon SO, Li L, Hsu YM, Ambrose C, et al. BAFF supports human B cell differentiation in the lymphoid follicles through distinct receptors. Int Immunol. 2005; 17(6):779–88. [PubMed: 15908449]
37. Belnoue E, Pihlgren M, McGaha TL, Tougne C, Rochat AF, Bossen C, et al. APRIL is critical for plasmablast survival in the bone marrow and poorly expressed by early-life bone marrow stromal cells. Blood. 2008; 111(5):2755–64. [PubMed: 18180376]
38. Avery DT, Kalled SL, Ellyard JI, Ambrose C, Bixler SA, Thien M, et al. BAFF selectively enhances the survival of plasmablasts generated from human memory B cells. J Clin Invest. 2003; 112(2):286–97. [PubMed: 12865416]
39. Merrill JT, Erkan D, Buyon JP. Challenges in bringing the bench to bedside in drug development for SLE. Nat Rev Drug Discov. 2004; 3(12):1036–46. [PubMed: 15573102]
40. Furie RA, Petri MA, Wallace DJ, Ginzler EM, Merrill JT, Stohl W, et al. Novel evidence-based systemic lupus erythematosus responder index. Submitted to Arthritis Care and Research.

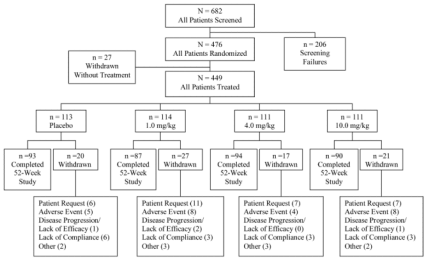

Figure 1.
Flow diagram of patient disposition during the study.

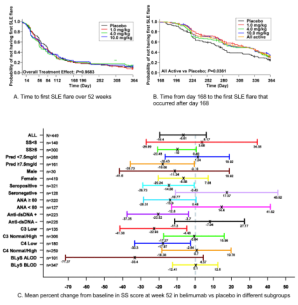

Figure 2. Time to first mild-moderate or severe flare as measured by the SLE Flare Index and subgroup analysis of response to 52-week SELENA-SLEDAI score

(A) All treated patients from weeks 0 to 52. Log-rank test for overall treatment effect; *P*=0.9683. (B) All patients from weeks 24–52. Log-rank test for combined belimumab vs placebo *P*= 0.0361. (C) Mean percent change from baseline in SELENA-SLEDAI score at week 52 in different subgroups. Each subgroup analyzed response rate between the all-belimumab-treatment group and the placebo group, where the absolute percent difference from placebo is set at 0 and the 95% confidence interval values are shown. SS = SELENA-SLEDAI; Pred = Prednisone; ANA = antinuclear antibodies; BLyS = B-lymphocyte stimulator; ALOD = above limit of detection (0.350 ng/mL); BLOD = below limit of detection

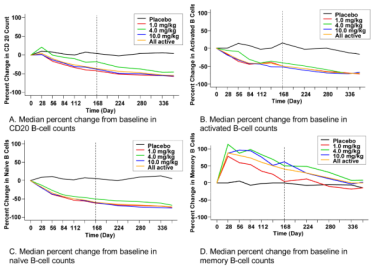

Figure 3. Percent change in B-cell subsets over 1 year of belimumab therapy or placebo added to standard of care therapy

(A) $CD20^+$ B cells, (B) naive ($CD20^{+/}27^-$) B cells, (C) activated ($CD20^+/69^+$), and (D) memory ($CD20^{+/}27^+$) B cells.

The baseline B-cell values in all 4 treatment groups were not significantly different. B-cell values are presented in absolute numbers for all patients combined: CD19 = 163.6/mm^3, CD 20 = 157.3/mm^3, naive = 120.4/mm^3, activated = 25.1/mm^3, memory = 36.6/mm^3, plasmacytoid = 6.6/mm^3 (not shown), and plasma cells = 3.9/mm^3 (not shown). B-cell subsets were unaffected in the placebo group by week 52, except for plasmacytoid cells, which declined by 33% (data not shown).

Table 1

Baseline demographic and clinical characteristics of enrolled patients (N=449)

	Placebo	Belimumab			
		1.0 mg/kg	4.0 mg/kg	10.0 mg/kg	All Active
	(n=113)	(n=114)	(n=111)	(n=111)	(n=336)
Female, %	90.3	93.9	94.6	94.6	94.3
Race					
Caucasian, %	70.8	71.9	67.6	70.3	69.9
African-American, %	20.4	21.1	27.9	25.2	24.7
Hispanic or Latino origin, %	18.6	14.9	21.6	18.9	18.5
Age, mean yr±SD	42.2±10.9	42.0±11.7	42.6±10.7	41.8±11.7	42.1±11.3
Disease duration, mean yr±SD	8.1±7.4	8.5±7.2	10.1±9.2	8.5±8.0	9.0±8.2
SELENA-SLEDAI, mean±SE	9.5±0.5	9.9±0.4	9.4±0.5	9.5±0.4	9.6±0.3
≥1 BILAG A or B score, %	90.3	95.6	96.4	97.5	95.8
PGA, mean±SE	1.4±0.05	1.6±0.05	1.5±0.05	1.5±0.05	1.5±0.03
Daily prednisone use, %	72.6	68.4	65.8	66.7	67.0
>7.5 mg/d at baseline, %	42.5	35.1	31.5	34.2	33.6
Immunosuppressive use,[a] %	48.7	45.6	53.2	52.3	50.3
Anti-malarial use, %	74.3	70.2	64.9	69.4	68.2
BLyS ALOD, %	43.4	43.0	44.1	43.2	43.5
ANA ≥1:80, %	74.3	70.2	73.9	66.7	70.2
Anti-dsDNA ≥30 IU/mL, %	51.3	51.8	47.7	47.7	49.1
Serologically active,[b] %	76.1	68.4	71.2	70.3	69.9
C3, mg/dL, mean±SE	114.6±3.4	110.0±3.6	109.4±3.0	112.7±3.5	110.7±2.0
C4, mg/dL, mean±SE	20.2±1.0	18.3±1.0	18.3±0.9	19.8±1.0	18.8±0.6
IgG, mg/dL, mean±SE	1366.8±55.1	1372.7±48.4	1385.4±48.8	1407.3±54.3	1388.3±29.1
IgA, mg/dL, mean±SE	300.8±18.6	285.2±15.4	278.2±15.3	303.8±14.9	289.0±8.8
IgM, mg/dL, mean±SE	101.5±6.9	117.7±8.1	127.6±9.7	103.2±7.1	116.2±4.9
IgE, KU/L, mean±SE	70.8±13.4	114.1±22.9	127.7±31.9	91.4±18.4	111.1±14.4
History of SLE disease manifestations (per ACR criteria)					
Arthritis, %	92.9	95.6	91.9	93.7	93.8

	Placebo	Belimumab			
		1.0 mg/kg	4.0 mg/kg	10.0 mg/kg	All Active
	(n=113)	(n=114)	(n=111)	(n=111)	(n=336)
Renal disorder, %	22.1	35.1	25.2	35.1	31.8
Neurologic disorder, %	8.0	9.6	12.6	7.2	9.8
Hematologic disorder, %	44.2	54.4	49.5	58.6	54.2
Immunologic disorder, %	71.7	74.6	72.1	72.1	72.9
ANA, %	98.2	96.5	99.1	96.4	97.3

[a] Excluding aminoquinoline anti-malarials (hydroxylchloroquine, chloroquine, quinacrine).

[b] ANA ≥1:80 and/or anti-dsDNA positive at screening and day 0.

SD = standard deviation; SE = standard error; BILAG = Bristish Isles Lupus Assessment Group; PGA = Physician's Global Assessment; BLyS = B-lymphocyte stimulator; ALOD = above limit of detection (0.350 ng/mL); ANA = antinuclear antibodies.

Arthritis Rheum. Author manuscript; available in PMC 2010 September 15.

Table 2

Summary of efficacy results for all patients (N=449) and for serologically active[a] patients (n=321)

	Placebo		Belimumab							
			1.0 mg/kg		4.0 mg/kg		10.0 mg/kg		All Active	
	All	Sero+	All	Sero+	All	Sero+	All	Sero+	All	Sero+
	n=113	n=86	n=114	N=78	n=111	n=79	n=111	n=78	n=336	n=235
DAIs										
% change from baseline, mean±SE										
SELENA-SLEDAI at week 24	−17.2±5.1	−15.6±5.9	−23.3±4.4	−25.5±5.0	−11.3±5.4	−6.8±6.5	−23.7±4.2	−30.0±4.5	−19.5±2.7	−20.7±3.2
SELENA-SLEDAI at week 52	−20.6±5.2	−14.2±6.1	−29.7±4.3	−34.3±4.2*	−23.9±7.3	−19.3±9.2	−27.9±5.5	−33.0±4.5*	−27.2±3.3	−28.8±3.7*
Modified SELENA-SLEDAI[b]	n=109	n=82	n=112	n=76	n=106	n=74	n=109	n=76	n=327	n=226
Modified SELENA-SLEDAI at week 0	7.9	7.7	7.9	7.7	7.9	7.6	7.8	7.5	7.9	7.6
Modified SELENA-SLEDAI at week 52	−23.9±7.4	−17.8±9.3	−37.1±4.8	−44.4±5.2*	−34.7±6.1	−33.0±7.4	−32.6±6.0	−40.1±5.4*	−34.8±3.3	−39.2±3.5*
PGA at week 52	−13.8±6.0	−10.7±7.7	−28.3±4.3*	−30.1±5.2*	−30.6±4.3*	−34.2±5.2*	−33.0±3.8*	−33.7±4.7*	−30.6±2.4*	−32.7±2.9*
SF-36 PCS at week 52	1.4±0.7	1.2±0.9	2.7±0.7	3.6±0.9	1.7±0.7	1.9±0.7	3.4±0.8*	3.5±0.9*	2.6±0.4	3.0±0.5*
Prednisone										
% Reduction[c]	27.1	30.8	20.0	23.3	31.4	37.9	44.7	50. 0	31.9	37.6
Dose reduction mg/day[d]										
Days 309–337	−1.7	−3.1	+0.4	+0.3	−2.6	−2.6	−6.4	−7.8	−3.1	−3.7
Days 337–364	−2.1	−3.4	+0.3	+0.4	−2.4	−2.7	−6.4	−7.8	−3.1	−3.8
% Increase to >7.5 mg/day[e]	12.3	12.8	12.2	14.6	6.6	8.0	2.7*	2.3	7.2	8.5
Immunosuppressive drug changes,[f] %										
Delete ≥1	5.3	4.7	5.3	5.1	5.4	2.5	2.7	1.3	4.5	3.0
No change	83.2	81.4	90.3	88.5	85.6	86.1	91.9*	91.0	89.3	88.5
Add ≥1	11.5	14.0	4.4*	6.4	9.0	11.4	5.4	7.7	6.2	8.5
Flares										
New 1A or 1B BILAG, %	35.4	39.5	33.3	35.9	28.8	26.6	26.1	25.6	29.5	29.4
Time to 1st flare over week 52,[g]	83	84	68	68	61	77	70	84	67	77
median days (IQR)	(42, 140)	(36, 148)	(39, 146)	(40, 146)	(29, 147)	(28, 173)	(29, 154)	(41, 168)	(32, 147)	(33, 154)

	Placebo		Belimumab							
			1.0 mg/kg		4.0 mg/kg		10.0 mg/kg		All Active	
	All n=113	Sero+ n=86	All n=114	Sero+ N=78	All n=111	Sero+ n=79	All n=111	Sero+ n=78	All n=336	Sero+ n=235
Time to 1st flare from weeks 24–52,[g]	108	111	154	170	135	167	152	126	154*	164
median days (IQR)	(56, 203)	(56, 203)	(71, 203)	(94, 210)	(56, −)	(56, −)	(59, −)	(59, 204)	(63, 210)	(63, −)
SLE flare from weeks 24–52,[g] %	72.8	71.4	67.7	64.2	66.4	62.7	63.9	65.2	66.0	64.0

*P <0.05, belimumab group compared with placebo

[a] ANA ≥1:80 and/or anti-dsDNA positive at screening and day 0.

[b] Modification of the SELENA-SLEDAI score (mean) by excluding the 2-point score contributions of both anti-dsDNA increase and low complement C3/C4 from the total SELENA-SLEDAI score. Patients with modified SELENA-SLEDAI score ≥2 at baseline.

[c] Patients with average dose reduced to ≤7.5 mg/day and/or reduced by a minimum of 50% from baseline during week 40 through week 52. The analysis was on patients with baseline prednisone dose >7.5 mg/day. (Number of patients per treatment group: placebo = 48, 1 mg/kg = 40, 4 mg/kg = 35, 10 mg/kg = 38 and all active = 113).

[d] Prednisone dose (mg/day) reduction over last 2 months of therapy in two 28-day time periods in patients with baseline prednisone dose >7.5 mg/day.

[e] Patients with average prednisone dose increased to >7.5 mg/day during last month of therapy 4 weeks prior to the week 52 visit in patients who had baseline prednisone ≤7.5 mg/day.

[f] Immunosuppressive drug changes (excluding anti-malarials) over 1 year study period.

[g] Mild/moderate or severe flare as measured by SLE Flare Index.

Sero+ = serologically active; PGA = Physician's Global Assessment; SF-36 PCS = Short Form 36 Physical Component Summary; IQR = interquartile range.

Table 3

Number of patients with treatment-emergent adverse events (N=449)[a]

		Placebo	Belimumab			
			1.0 mg/kg	4.0 mg/kg	10.0 mg/kg	All Active
		n=113	n=114	n=111	n=111	n=336
≥1 AE		97.3	97.4	96.4	97.3	97.0
≥1 serious AE		19.5	18.4	13.5	16.2	16.1
Infections and infestations		72.6	74.6	79.3	73.0	75.6
≥1 serious[b] infection AE		3.5	6.1	6.3	2.7	5.1
≥1 severe[b] infection AE		2.7	7.0	5.4	3.6	5.4
By MedDRA SOC >40% in all-active group						
Musculoskeletal and connective tissue disorders		70.8	64.9	64.0	68.5	65.8
Skin and subcutaneous tissue disorders		50.4	63.2	58.6	49.6	57.1
Gastrointestinal disorders		55.8	55.3	54.1	57.7	55.7
Nervous system disorders		46.9	43.9	51.4	54.1	49.7
General disorders and administration site conditions		54.9	41.2	57.7	48.7	49.1
Respiratory, thoracic, and mediastinal disorders		46.0	44.7	34.2	44.1	41.1
Treatment-emergent AEs ≥15% in all-active group						
Arthralgia		37.2	36.0	33.3	36.9	35.4
Upper respiratory tract infection		29.2	31.6	32.4	26.1	30.1
Headache		23.9	25.4	27.9	31.5	28.3
Fatigue		31.0	23.7	29.7	24.3	25.9
Nausea		23.9	27.2	19.8	29.7	25.6
Diarrhea		16.8	16.7	20.7	15.3	17.6
Arthritis		16.8	14.0	18.9	16.2	16.4
Urinary tract infection		15.9	14.0	17.1	18.0	16.4
Laboratory abnormalities >2% in all active group						
	Grade	**(n=112)**	**(n=114)**	**(n=110)**	**(n=111)**	**(n=335)**
WBC	3	2.7	3.5	4.5	4.5	4.2
Neutrophils	3	5.4	3.5	8.2	6.3	6.0
	4	-	0.9	0.9	0.9	0.9

		Placebo	Belimumab			
			1.0 mg/kg	4.0 mg/kg	10.0 mg/kg	All Active
		n=113	n=114	n=111	n=111	n=336
Hemoglobin	3	3.6	4.4	3.6	0.9	3.0
	4	-	-	0.9	-	0.3
Prothrombin time[c]	3	4.5	5.3	11.8	9.0	8.7
	4	8.0	6.2	8.2	6.3	6.9
24-hour urinary protein	3	5.4	5.3	4.6	6.4	5.4
	4	3.6	2.7	1.8	3.6	2.7
Hypogammaglobulinemia[d]	3	0	2.7	2.7	0	1.8

[a] Except where indicated otherwise, values are percentage (%).

[b] Includes life-threatening. Listings of serious and severe infections:

* denotes events graded both serious and severe

[indicates 2 events for the same patient]

Placebo: wound infection, viral infection, furuncle,* bilateral pneumonia. Severe only: herpes zoster, pneumonia.

Belimumab 1 mg/kg: gastroenteritis viral,* bronchitis acute, lobar pneumonia,* cellulitis, [septic arthritis-streptobacillus* and cellulitis], pneumonia* (2 patients), pneumonia-bacterial.* Severe only: urinary tract infection, infected skin ulcer.

Belimumab 4 mg/kg: [cellulitis* and pneumonia, pneumonia],* streptococcal bacteremia, [bronchitis acute* and UTI], pyelonephritis acute, viral infection, West Nile viral infection.* Severe only: upper respiratory tract infection (URI) (2 patients).

Belimumab 10 mg/kg: herpes zoster, anal infection,* clostridium colitis, sepsis.* Severe only: URI, postoperative infection

[c] 11.9% of belimumab- and 8.9% of placebo-treated patients were receiving warfarin; 18 patients with grade 3/4 PT were not on warfarin and only 2 of these patients (1 placebo and 110 mg/kg belimumab) had >1 prolonged PT value during the study.

[d] Grade 3 = <400 mg/dL IgG. Four of the six patients had IgG levels below lower limit of normal (LLN) at baseline and only one patient had at least a grade 2 shift from grade 0 to3. Overall, the % of patients who had immunoglobulin levels below the LLN at baseline compared to week 52 were as follows: IgG, 5.3% to 6.4% placebo versus. 5.7% to 7.2% belimumab (all active); for IgA, 7.1% to 7.4% placebo versus. 5.7% to 8.3% belimumab (all active); and IgM, 17.7% to 19.4% placebo versus. 14.7% to 31.4% belimumab (all active).

MedDRA SOC = Medical Dictionary for Regulatory Activities system organ class; PT = prothrombin time; WBC = white blood cells.