ORIGINAL ARTICLE

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

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

Methods. Patients with a Safety of Estrogens in Lupus Erythematosus: National Assessment (SELENA) version of the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score ≥4 (n = 449) were randomly assigned to belimumab (1, 4, or 10 mg/kg) or placebo in a 52-week study. Coprimary end points were the percent change in the SELENA–SLEDAI score at week 24 and the time to first SLE flare.

Results. Significant differences between the treatment and placebo groups were not attained for either primary end point, and no dose response was observed. Reductions in SELENA–SLEDAI scores from baseline were 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 (antinuclear antibody titer ≥1:80 and/or anti–double-stranded DNA [anti-dsDNA] ≥30 IU/ml), belimumab treatment resulted in significantly better responses at week 52 than placebo for SELENA–SLEDAI score (-28.8% versus -14.2%; $P = 0.0435$), physician's global assessment (-32.7% versus -10.7%; $P = 0.0011$), and Short Form 36 physical component score ($+3.0$ versus $+1.2$ points; $P = 0.0410$). Treatment with belimumab resulted in a 63–71% reduction of naive, activated, and plasmacytoid CD20+ B cells, and a 29.4% reduction in anti-dsDNA titers ($P = 0.0017$) by week 52. The rates of adverse events and serious adverse events were similar in the belimumab and placebo groups.

Conclusion. Belimumab was biologically active and well tolerated. The effect of belimumab 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 to SOC alone.

INTRODUCTION

B lymphocyte stimulator (BLyS; trademark of Human Genome Sciences, Rockville, MD), a 285–amino acid protein member of the tumor necrosis factor ligand superfamily, is a key B cell survival factor (1) and binds 3 membrane receptors (TACI, BCMA, and BAFF-R/B lymphocyte stimulator receptor 3 [BR-3]) 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 the development of clinical disease (9). Moreover, soluble BLyS receptors (TACI-Fc or BR-3-Fc) administered to SLE-prone (NZB × NZW)F$_1$ 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 messenger RNA expression correlate with changes in SLE disease activity and anti–double-stranded DNA (anti-dsDNA) antibody titers (11,14–16).

Belimumab is a fully human IgG1λ monoclonal antibody that binds to soluble human BLyS and inhibits its biologic activity (17,18). In a phase I dose-escalation study performed in 70 patients with SLE, no related serious adverse events (AEs) or safety signals were reported, and evidence of biologic 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 biologic 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 the effects of belimumab 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, and 28, and then every 28 days for 52 weeks plus SOC. Hematology, chemistry,

urinalysis, 24-hour urine collection, biologic markers, autoantibodies, SLE disease activity scales (the Safety of Estrogens in Lupus Erythematosus: National Assessment [SELENA] version of the Systemic Lupus Erythematosus Disease Activity Index [SLEDAI] [20], the SELENA–SLEDAI flare index [SFI] [21], and the British Isles Lupus Assessment Group [BILAG] instrument [22,23]), physician's global assessment (PGA), and the Short Form 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 patients (age ≥18 years) fulfilling the American College of Rheumatology (ACR) criteria for SLE who had active disease as defined by a SELENA–SLEDAI score of ≥4 at screening were eligible for enrollment (25). Inclusion criteria mandated a history of measurable autoantibodies (including any of the following: antinuclear antibodies [ANAs], anti-dsDNA, anti-Sm, anti-RNP, anti-Ro, anti-La, or anticardiolipin), but they did not have to be present at screening. In addition, adult patients were required to be receiving a stable regimen of prednisone (5–40 mg/day), antimalarials, or immunosuppressive agents 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, biologics, cyclophosphamide, or dosages 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 coprimary efficacy end points were the percent change in the SELENA–SLEDAI score from baseline (day 0) to week 24 and the time to first mild/moderate or severe flare as defined by the SFI (21) during 52 weeks. Secondary efficacy end points included changes in week 52 SELENA–SLEDAI and BILAG scores, time to first SLE flare (assessed by the SFI or BILAG) during and after the first 24 weeks, and the percentage of patients with a prednisone dosage ≤7.5 mg/day or reduced by 50% from baseline during weeks 40–52. Other secondary efficacy end points 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 immunoglobulin levels. Exploratory analyses were performed to identify subgroups with superior treatment responses.

Biologic 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). ANAs were determined by a screening enzyme-linked immunosorbent assay, 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 facility (Nichols Labo-

ratory, 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+], and plasmacytoid [CD20+/CD138+]) and plasma cells (CD20−/CD138+ and CD20−/CD27^{high}), 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 method. The analysis of primary efficacy end points was performed in a modified intent-to-treat population, defined as all patients who were randomized and received a dose of the study agent. Discrete variables were analyzed using a likelihood chi-square test and continuous variables were analyzed using the Student's *t*-test or the Wilcoxon's rank sum test, as appropriate.

The sample size was based on the 2 coprimary efficacy end points. 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 the SELENA–SLEDAI (assuming an average decrease of 25% from baseline in the placebo group with an SD of 50%) at week 24, and 2) a reduction in the percentage of patients having their first SLE flare by week 52 from 65% in the placebo group to 43% in any 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 was administered to 113 patients at 59 sites in the US and Canada from October 2003 to August 2005 (Figure 1). There were no

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

significant differences among treatment groups in baseline features (Table 1) or in reasons for discontinuation (Figure 1).

Primary clinical end points. *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 the SELENA–SLEDAI scores from baseline to weeks 24 or 52. Mean percent changes in SELENA–SLEDAI scores were −19.5% for the combined belimumab groups versus −17.2% for the placebo group at 24 weeks, and −27.2% for the belimumab-treated groups versus −20.6% for the placebo group at 52 weeks (Table 2). Dose-dependent effects on changes in the 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 an SLE flare (mild/moderate or severe) by weeks 12, 24, and 52, respectively, and there were no dose-dependent differences among the 4 treatment groups (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 rates were 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 the time to first SFI-defined flare over 52 weeks between the combined belimumab and placebo groups (67 versus 83 days) (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 patients and in 17% of placebo-treated patients ($P = 0.1807$).

Secondary and exploratory clinical end points in all patients. *Corticosteroid dose and immunosuppressive agents.* Among patients whose baseline prednisone dosage was >7.5 mg/day, 44.7% of patients receiving 10 mg/kg of belimumab were able to reduce their steroid dosage 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 dosage during the last 2 months of the study was reduced by 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 treatment group receiving 10 mg/kg of belimumab having the best response (6.4 mg/day [−40.5%]; $P = 0.2218$). In patients receiving either no steroids or low-dose steroids (≤7.5 mg/day) at baseline, 2.7% of the patients treated with 10 mg/kg of belimumab (compared with 12.3% of placebo patients; $P = 0.0459$) (Table 2) had their average prednisone dosage increased to >7.5 mg/day. Over 52
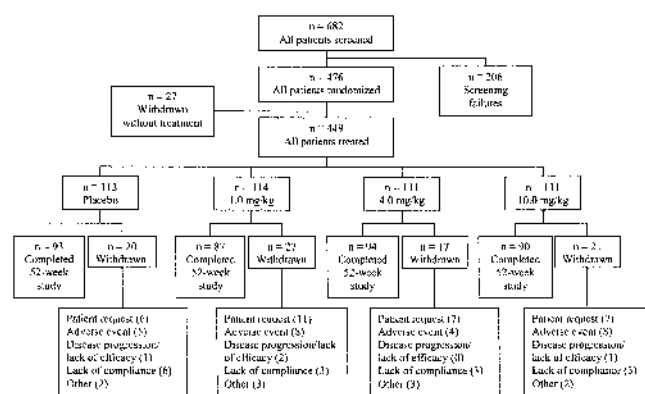
Table 1. Baseline demographic and clinical characteristics of the enrolled patients (n = 449)*					
		Belimumab			
	Placebo (n = 113)	1.0 mg/kg (n = 114)	4.0 mg/kg (n = 111)	10.0 mg/kg (n = 111)	All active (n = 336)
Women	90.3	93.9	94.6	94.6	94.3
Race					
White	70.8	71.9	67.6	70.3	69.9
African American	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 ± SD years	42.2 ± 10.9	42.0 ± 11.7	42.6 ± 10.7	41.8 ± 11.7	42.1 ± 11.3
Disease duration, mean ± SD years	8.1 ± 7.4	8.5 ± 7.2	10.1 ± 9.2	8.5 ± 8.0	9.0 ± 8.2
SELENA–SLEDAI score, mean ± SEM	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 ± SEM	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/day at baseline	42.5	35.1	31.5	34.2	33.6
Immunosuppressive agent use†	48.7	45.6	53.2	52.3	50.3
Antimalarial use	74.3	70.2	64.9	69.4	68.2
BLyS ALOD	43.4	43.0	44.1	43.2	43.5
ANA titer ≥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‡	76.1	68.4	71.2	70.3	69.9
C3, mean ± SEM mg/dl	114.6 ± 3.4	110.0 ± 3.6	109.4 ± 3.0	112.7 ± 3.5	110.7 ± 2.0
C4, mean ± SEM mg/dl	20.2 ± 1.0	18.3 ± 1.0	18.3 ± 0.9	19.8 ± 1.0	18.8 ± 0.6
IgG, mean ± SEM mg/dl	1,366.8 ± 55.1	1,372.7 ± 48.4	1,385.4 ± 48.8	1,407.3 ± 54.3	1,388.3 ± 29.1
IgA, mean ± SEM mg/dl	300.8 ± 18.6	285.2 ± 15.4	278.2 ± 15.3	303.8 ± 14.9	289.0 ± 8.8
IgM, mean ± SEM mg/dl	101.5 ± 6.9	117.7 ± 8.1	127.6 ± 9.7	103.2 ± 7.1	116.2 ± 4.9
IgE, mean ± SEM KU/liter	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
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

* Values are the percentage unless otherwise indicated. SELENA–SLEDAI = Safety of Estrogens in Lupus Erythematosus: National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index; BILAG = British Isles Lupus Assessment Group; PGA = physician's global assessment; BLyS = B lymphocyte stimulator; ALOD = above limit of detection (0.350 ng/ml); ANA = antinuclear antibody; anti-dsDNA = anti–double-stranded DNA; KU = Kunitz units; SLE = systemic lupus erythematosus; ACR = American College of Rheumatology.
† Excluding aminoquinoline antimalarials (hydroxychloroquine, chloroquine, and quinacrine).
‡ ANA titer ≥1:80 and/or anti-dsDNA positive at screening and day 0.

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.

PGA and SF-36 physical component summary (PCS) score. 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 SF-36 PCS (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 a 10 mg/kg dose of belimumab were observed (*P* = 0.0167) (Table 2). An increase of ≥2.5 points from baseline in the PCS is con-

sidered to be the minimum clinically important difference (28).

BILAG. The incidence of new A or B organ system domain flares in the combined belimumab group was similar to that 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. 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 dosage >7.5 mg/day, and serologic activity (ANA titer ≥1:80 or anti-dsDNA antibodies >30 IU/ml) at both screening and day 0 (Figure 2C). Baseline

Table 2. Summary of efficacy results for all patients (n = 449) and for serologically active patients (n = 321)*									
	Placebo		Belimumab 1.0 mg/kg		Belimumab 4.0 mg/kg		Belimumab 10.0 mg/kg		All active belimumab	
	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)
Disease activity indices										
% change from baseline										
SELENA–SLEDAI score at week 24, mean ± SEM	−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 score at week 52, mean ± SEM	−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 score, no.§	109	82	112	76	106	74	109	76	327	226
Modified SELENA–SLEDAI score at week 0, mean	7.9	7.7	7.9	7.7	7.9	7.6	7.8	7.5	7.9	7.6
Modified SELENA–SLEDAI score at week 52, mean ± SEM	−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, mean ± SEM	−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, mean ± SEM	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, %¶	27.1	30.8	20.0	23.3	31.4	37.9	44.7	50.0	31.9	37.6
Dosage reduction, mg/day#										
Days 309–336	−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, %**	12.3	12.8	12.2	14.6	6.6	8.0	2.7‡	2.3	7.2	8.5
Immunosuppressive agent changes, %††										
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, median (IQR) days‡‡	83 (42, 140)	84 (36, 148)	68 (39, 146)	68 (40, 146)	61 (29, 147)	77 (28, 173)	70 (29, 154)	84 (41, 168)	67 (32, 147)	77 (33, 154)
Time to 1st flare from weeks 24–52, median (IQR) days‡‡	108 (56, 203)	111 (56, 203)	154 (71, 203)	170 (94, 210)	135 (56, −)	167 (56, −)	152 (59, −)	126 (59, 204)	154 (63, 210)‡	164 (63, −)
SLE flare from weeks 24–52, %‡‡	72.8	71.4	67.7	64.2	66.4	62.7	63.9	65.2	66.0	64.0

* SELENA–SLEDAI = Safety of Estrogens in Lupus Erythematosus: National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index; PGA = physician's global assessment; SF-36 PCS = Short Form 36 physical component summary; BILAG = British Isles Lupus Assessment Group; IQR = interquartile range; − = data could not be estimated; SLE = systemic lupus erythematosus.
† Serologically active; antinuclear antibody titer ≥1:80 and/or anti–double-stranded DNA (anti-dsDNA) positive at screening and day 0.
‡ Belimumab group compared with placebo: $P < 0.05$.
§ Modification of the SELENA–SLEDAI score (mean) by excluding the 2-point score contributions of both anti-dsDNA increase and low C3/C4 from the total SELENA–SLEDAI score. Number of patients with modified SELENA–SLEDAI scores ≥2 at baseline.
¶ Patients with average dosage 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 performed on patients with a baseline prednisone dosage of 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.)
# Prednisone dosage (mg/day) reduction over last the 2 months of therapy in two 28-day time periods in patients with a baseline prednisone dosage of >7.5 mg/day.
** Patients with an average prednisone dosage increased to >7.5 mg/day during the last month of therapy 4 weeks prior to the week 52 visit in patients who had a baseline prednisone dosage of ≤7.5 mg/day.
†† Immunosuppressive agent changes (excluding antimalarials) over the 1-year study period.
‡‡ Mild/moderate or severe flare as measured by the SELENA–SLEDAI flare index.
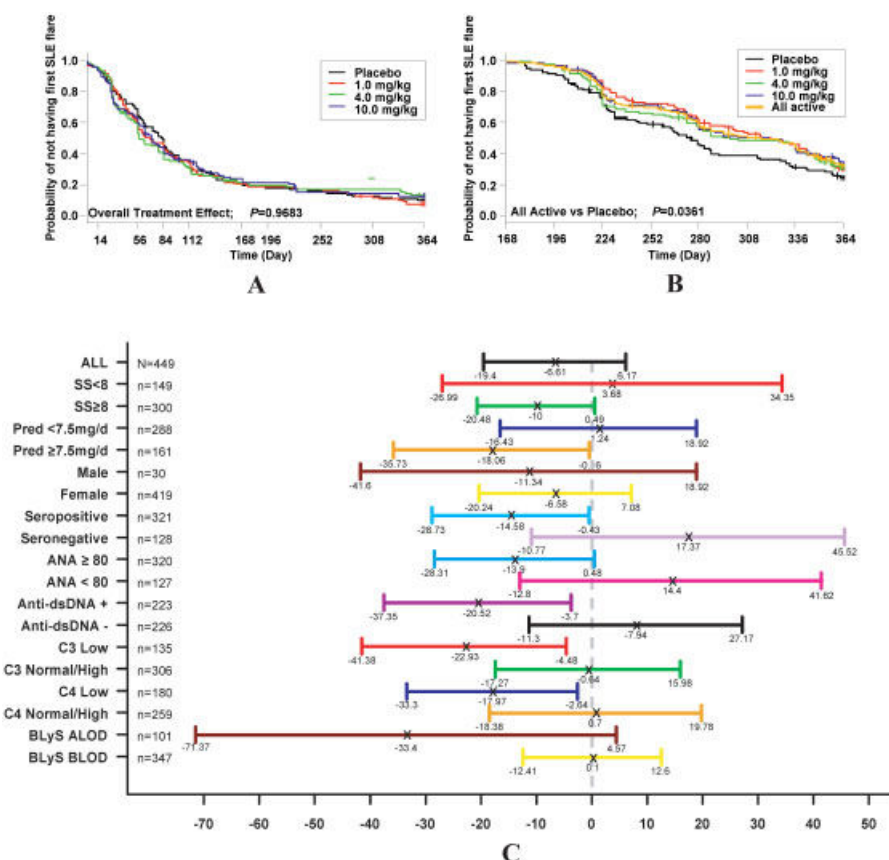
Figure 2. Time to first mild/moderate or severe flare as measured by the Safety of Estrogens in Lupus Erythematosus: National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index (SS) flare index and subgroup analysis of response to the 52-week SS score. **A**, Time to first systemic lupus erythematosus (SLE) flare for all treated patients from weeks 0 to 52 (log rank test for overall treatment effect: P = 0.9683). **B**, Time from day 168 to the first SLE flare that occurred after day 168 for all patients (log rank test for combined belimumab vs. placebo: P = 0.0361). **C**, Mean percent change from baseline in SS score at week 52 in different subgroups (belimumab vs. placebo). Each subgroup analyzed the response rate between the groups treated with belimumab and the placebo group, where the absolute percent difference from placebo is set at 0 and the 95% confidence interval values are shown. Pred = prednisone; ANA = antinuclear antibody; anti-dsDNA = anti–double-stranded DNA; BLyS = B lymphocyte stimulator; ALOD = above limit of detection (0.350 ng/ml); BLOD = below limit of detection.

characteristics associated with favorable trends in SELENA–SLEDAI scores (a mean difference between belimumab treatment and placebo of a ≥10% reduction, but not statistically significant) were SELENA–SLEDAI scores ≥8, an ANA titer of ≥1:80 at both screening and day 0, and elevated BLyS levels at day 0.

Biologic 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 immunoglobulin 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/mm³, and by week 52, the percent changes were −49.3% for CD19+, −54.1% for CD20+, −70.8% for naive

B cells, −70.4% for activated B cells, and −62.5% for plasmacytoid B cells. Conversely, in the combined belimumab group, the percent change in the median value of memory B cells was increased by 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 between the belimumab treatment group and the placebo group (−18.2% versus +28.6%; P = 0.0027). No significant group differences were noted in the changes in plasma cells between the 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 immunoglobulin 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 immunoglobulin isotypes. There was a significantly greater number of patients re-
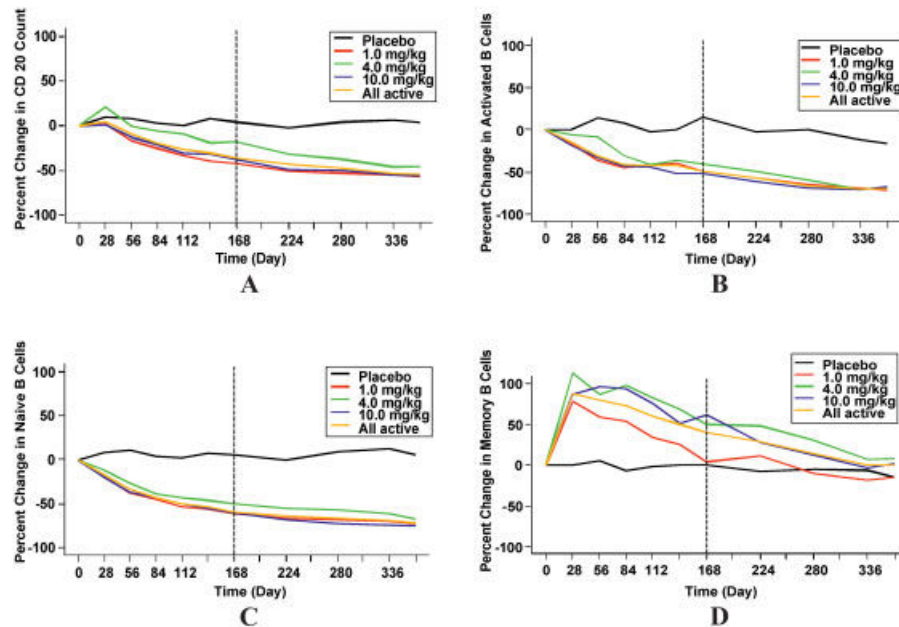
Figure 3. Median percent change in B cell subsets over 1 year of belimumab therapy or placebo added to standard of care therapy in **A**, CD20+ B cells, **B**, activated (CD20+/CD27−) B cells, **C**, naive (CD20+/CD69+) B cells, and **D**, memory (CD20+/CD27+) B cells. The baseline B cell values in all 4 treatment groups were not significantly different. B cell values are shown in absolute numbers for all patients combined: CD19 = 163.6/mm³, CD20 = 157.3/mm³, naive = 120.4/mm³, activated = 25.1/mm³, memory = 36.6/mm³, plasmacy-toid = 6.6/mm³ (not shown), and plasma cells = 3.9/mm³ (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).

ceiving belimumab (31.4% versus 19.4% receiving placebo; *P* < 0.0192) who had low IgM at week 52, but not IgG or IgA (Table 3).

ANAs and complement levels. 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-treated patients at week 52 (*P* = 0.0119). Median changes in C4 levels 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 levels at week 52 were −2.1% in the belimumab-treated patients versus −6.5% in the placebo group (*P* = 0.0362), and +6.3% in patients with low (<90 mg/dl) C3 concentrations at baseline versus −0.8% in the placebo group (*P* = 0.15).

Safety and tolerability. During the 52-week study and 8-week followup period, the incidences of AEs by individual event or Medical Dictionary for Regulatory Activities 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 patients treated with belimumab (4% versus 0%). No significant dose-related increase in AEs was ob-

served. Serious AEs occurred in 19.5% of placebo patients compared with 16.1% of patients in the 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 of belimumab groups, respectively) were reported, and neither was 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 receiving 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. There were 321 serologically active patients 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 (age 41 versus 46 years; *P* < 0.0001), had more major organs involved (e.g., 34% versus 19% renal and 59% versus 33% hematologic), fewer cutaneous manifestations, higher mean SELENA–SLEDAI scores (9.8 versus 8.9), greater prednisone use

Table 3. Number of patients with treatment-emergent AEs (n = 449)*					
		Belimumab			
	Placebo (n = 113)	**1.0 mg/kg (n = 114)**	**4.0 mg/kg (n = 111)**	**10.0 mg/kg (n = 111)**	**All active (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 infection AE#	3.5	6.1	6.3	2.7	5.1
≥1 severe infection AE#	2.7	7.0	5.4	3.6	5.4
By MedDRA system organ class >40% in the 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 the 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 the all active group, no.	112	114	110	111	335
White blood cells					
Grade 3	2.7	3.5	4.5	4.5	4.2
Neutrophils					
Grade 3	5.4	3.5	8.2	6.3	6.0
Grade 4	–	0.9	0.9	0.9	0.9
Hemoglobin					
Grade 3	3.6	4.4	3.6	0.9	3.0
Grade 4	–	–	0.9	–	0.3
Prothrombin time**					
Grade 3	4.5	5.3	11.8	9.0	8.7
Grade 4	8.0	6.2	8.2	6.3	6.9
24-hour urinary protein					
Grade 3	5.4	5.3	4.6	6.4	5.4
Grade 4	3.6	2.7	1.8	3.6	2.7
Hypogammaglobulinemia††					
Grade 3	0	2.7	2.7	0	1.8

* Values are the percentage unless otherwise indicated. AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities.
† Placebo serious and severe infections: wound infection, viral infection, bilateral pneumonia, herpes zoster (severe only), pneumonia (severe only), and furuncle (graded serious and severe).
‡ Belimumab 1.0 mg/kg serious and severe infections: acute bronchitis, cellulitis, urinary tract infection (severe only), infected skin ulcer (severe only), viral gastroenteritis (graded serious and severe), lobar pneumonia (graded serious and severe), pneumonia (graded serious and severe; 2 patients), septic arthritis-streptobacillus (graded serious and severe) and cellulitis (2 events for the same patient), and bacterial pneumonia (graded serious and severe).
§ Belimumab 4.0 mg/kg serious and severe infections: streptococcal bacteremia, acute pyelonephritis, viral infection, upper respiratory tract infection (severe only; 2 patients), cellulitis (graded serious and severe) and pneumonia (graded serious and severe; 2 events for the same patient), acute bronchitis (graded serious and severe) and urinary tract infection (2 events for the same patient), and West Nile viral infection (graded serious and severe).
¶ Belimumab 10.0 mg/kg serious and severe infections: herpes zoster, clostridium colitis, upper respiratory tract infection (severe only), postoperative infection (severe only), anal infection (graded serious and severe), and sepsis (graded serious and severe).
# Includes life-threatening events.
** A total of 11.9% of belimumab-treated patients and 8.9% of placebo-treated patients were receiving warfarin; 18 patients with grade 3/4 prothrombin time were not receiving warfarin, and only 2 of these patients (1 placebo and 1 belimumab 10 mg/kg) had >1 prolonged prothrombin time value during the study.
†† Grade 3 = <400 mg/dl of IgG. Four of the 6 patients had IgG levels below the lower limit of normal at baseline, and only 1 patient had at least a grade 2 shift from grade 0 to 3. Overall, the percentage of patients who had immunoglobulin levels below the lower limit of normal at baseline compared with week 52 were as follows: IgG: 5.3–6.4% placebo vs. 5.7–7.2% belimumab (all active); IgA: 7.1–7.4% placebo vs. 5.7–8.3% belimumab (all active); and IgM: 17.7–19.4% placebo vs. 14.7–31.4% belimumab (all active).

(72.6% versus 57.8%; $P = 0.0027$), lower C3 and C4 levels ($P < 0.0001$), higher immunoglobulin levels (IgG, IgA, and IgE; all $P \leq 0.001$), lower baseline CD19+ and CD20+ B cell counts ($P \leq 0.01$), 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 modified SELENA–SLEDAI scoring that excluded contributions of anti-dsDNA and low complement levels (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 the 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 the BILAG composite score (data not shown). However, there were fewer new BILAG A or B flares in the combined belimumab group than in the placebo group (29.4% versus 39.5%; $P = 0.0871$) (Table 2). An 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 patients and all patients (data not shown), or between serologically active patients and seronegative 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 improvements compared with placebo as assessed by the coprimary end points of SELENA–SLEDAI score reduction at week 24 or reduction in the 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 score, and 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. This 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 benefits as measured by the 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 (OCs) (20), contraceptive methods (CMs) (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 intrauterine device), 64% (HRT), and 51% (HRT placebo). The high early flare rate in our study made it difficult to detect an effect, and it 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 end points. Prednisone use was lower in the belimumab groups, as evidenced by greater percentages of patients having reduced prednisone by $\geq 50\%$ or to <7.5 mg/day, and fewer patients required an increase to >7.5 mg/day than those 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 titer of $\geq 1:80$ 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 a significant improvement in the 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. Therefore, 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 receiving 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/BR-3 expression on plasma cells than on CD20+ B cells (34–36), and plasmablasts appear more dependent on APRIL for bone marrow survival (37). One year of belimumab therapy led to a 29% reduction in IgG anti-dsDNA antibodies 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 draft guidance document on the development of therapies for SLE, a novel combined end point based on 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.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Wallace had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study conception and design. Wallace, Stohl, Furie, McKay, Petri, Fernandez, Chevrier, Zhong, Freimuth.
Acquisition of data. Wallace, Stohl, Furie, Lisse, McKay, Merrill, Petri, Ginzler, Chatham, McCune, Fernandez, Chevrier, Zhong, Freimuth.

Analysis and interpretation of data. Wallace, Stohl, Furie, Merrill, Petri, Ginzler, McCune, Chevrier, Zhong, Freimuth.

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