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A Phase III, Randomized, Placebo-Controlled Study of Belimumab, a Monoclonal Antibody That Inhibits B Lymphocyte Stimulator, in Patients With Systemic Lupus Erythematosus

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Objective. **To assess the efficacy/safety of the B lymphocyte stimulator inhibitor belimumab plus standard therapy compared with placebo plus standard therapy in active systemic lupus erythematosus (SLE).**

Methods. **In a phase III, multicenter, randomized, placebo-controlled trial, 819 antinuclear antibody–positive or anti–double-stranded DNA–positive SLE patients with scores ≥6 on the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) version of the SLE Disease Activity Index (SLEDAI)**

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were randomized in a 1:1:1 ratio to receive 1 mg/kg belimumab, 10 mg/kg belimumab, or placebo intravenously on days 0, 14, and 28 and then every 28 days for 72 weeks. The primary efficacy end point was the SLE Responder Index (SRI) response rate at week 52 (an SRI response was defined as a ≥4-point reduction in SELENA–SLEDAI score, no new British Isles Lupus Assessment Group [BILAG] A organ domain score and no more than 1 new BILAG B score, and no worsening in physician's global assessment score versus baseline).

Results. **Belimumab at 10 mg/kg plus standard therapy met the primary efficacy end point, generating a significantly greater SRI response at week 52 compared with placebo (43.2% versus 33.5%; $P = 0.017$). The rate with 1 mg/kg belimumab was 40.6% ($P = 0.089$). Response rates at week 76 were 32.4%, 39.1%, and 38.5% with placebo, 1 mg/kg belimumab, and 10 mg/kg belimumab, respectively. In post hoc sensitivity analyses evaluating higher SELENA–SLEDAI score thresholds, 10 mg/kg belimumab achieved better discrimination at weeks 52 and 76. Risk of severe flares over 76 weeks (based on the modified SLE Flare Index) was reduced with 1 mg/kg belimumab (34%) ($P = 0.023$) and 10 mg/kg belimumab (23%) ($P = 0.13$). Serious and severe adverse events, including infections, laboratory abnormalities, malignancies, and deaths, were comparable across groups.**

Conclusion. **Belimumab plus standard therapy significantly improved SRI response rate, reduced SLE disease activity and severe flares, and was generally well tolerated in SLE.**

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder that affects a variety of organ systems and markedly impairs health-related quality of life (1–4). While available therapies, such as corticosteroids, hydroxychloroquine, and immunosuppressive drugs, have improved the outcomes of patients with SLE, there remains a significant unmet need for safe and more effective treatments. A novel approach to addressing immune abnormalities in SLE is to inhibit B lymphocyte stimulator (BLyS; also known as BAFF), a key survival cytokine for B cells (5–8). Overexpression of BLyS promotes survival of B cells (including autoreactive B cells), whereas inhibition of BLyS results in autoreactive B cell apoptosis (9,10). Elevated circulating BLyS levels are common in SLE and correlate with increased SLE disease activity and elevated anti–double-stranded DNA (anti-dsDNA) antibody concentrations (11–13).

Belimumab is a human IgG1λ monoclonal antibody that binds soluble human BLyS and inhibits its biologic activities. The clinical and pharmacodynamic effects of belimumab were evaluated in a phase II study in patients with active SLE who were receiving standard therapies (14). Reductions in circulating CD20+ B lymphocytes, short-lived plasma cells, and anti-dsDNA antibody titers were observed. A post hoc analysis identified a subset of autoantibody-positive (antinuclear antibody [ANA] titer ≥1:80 and/or anti-dsDNA antibody level ≥30 IU/ml) patients (71.5% of the original cohort) in whom belimumab reduced SLE disease activity as compared with placebo. In a 5-year, open-label extension of that study, improvement in SLE disease activity was sustained in the autoantibody-positive subset that continued receiving treatment (15). Furthermore, flare frequencies and autoantibody levels declined, and rates of adverse events (AEs), including infectious and serious AEs, remained stable or decreased over the 5-year period. Post hoc analysis of the phase II results led to the development of the SLE Responder Index (SRI), which reflects improvement in disease activity using a global scoring system while simultaneously requiring that there be no worsening of the disease in any organ system or by physician judgment (16).

With the SRI at week 52 as the primary end point, belimumab was evaluated in two phase III trials comparing belimumab at 1 and 10 mg/kg plus standard therapy with placebo plus standard therapy in patients with autoantibody-positive active SLE. In BLISS-52, a 52-week trial conducted primarily in Asia, South America, and Eastern Europe, belimumab was well tolerated, reduced SLE disease activity, prevented flares, improved serologic activity in patients with serologically active disease, and reduced corticosteroid use (17). BLISS-76, the second phase III clinical trial of belimumab in SLE, was conducted primarily in North America and Europe. Treatment continued through week 72, with the final evaluation at week 76. The results on efficacy, safety, tolerability, and biologic markers are presented from the BLISS-76 trial.

PATIENTS AND METHODS

Study design. In this phase III, multicenter, randomized, double-blind, placebo-controlled trial, patients with SLE receiving standard therapy were assigned to receive either placebo or 1 or 10 mg/kg belimumab by intravenous (IV) infusion over 1 hour on days 0, 14, and 28 and every 28 days through week 72. While the initiation of an immunosuppressive drug was prohibited during the trial, the addition of a new antimalarial drug and dosage increases of concomitant immunosuppressive or antimalarial drugs were permitted until week 16. After week 16, however, the maximum doses of immuno-

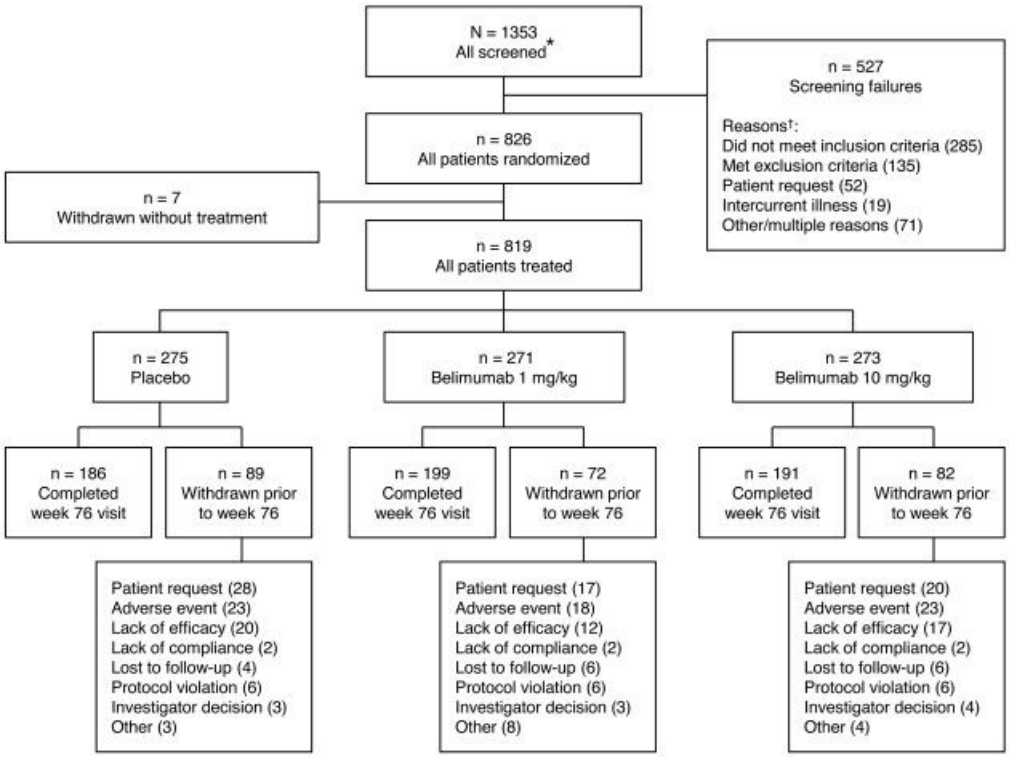

Figure 1. Flow diagram of patient disposition during the study. * = May count patients more than once if rescreened. † = Multiple reasons for some patients.

suppressive or antimalarial drugs could be no greater than the higher of the baseline or the week 16 dose. For corticosteroids, any dose was permitted through week 24; thereafter through week 44, the dose had to be within 25% or 5 mg of the baseline dose. Between weeks 44 and 52, no increase over the higher of the baseline or the week 44 dose was permitted. From weeks 52 through 68, the dose had to be within 25% or 5 mg of the baseline dose, and an increase over the higher of the baseline or the week 68 dose was prohibited after week 68. Prednisone could be reduced at the discretion of the investigator. As in the companion phase III BLISS-52 trial, the addition of a new biologic agent at any time, an inhibitor of the renin–angiotensin system after 4 months, or a new 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor after 6 months was prohibited; other antihypertensive or lipid-lowering agents were allowed during the study (17).

The Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) version of the SLE Disease Activity Index (SLEDAI) (18), the physician's global assessment of disease activity on a 0–10-cm visual analog scale, anchored at 0 (none) and 3 (severe), with intermediate lines at 1 (mild) and 2 (moderate) (18), the British Isles Lupus Assessment Group (BILAG) index (19,20), and the SLE Flare Index (21) were evaluated every 4 weeks (except weeks 56 and 64), as were AEs, vital signs, concomitant medications, and laboratory and pregnancy test results.

Entry criteria. Enrolled patients were required, at a minimum, to meet the following criteria: 1) age ≥18 years, 2) a diagnosis of SLE according to the American College of Rheumatology revised criteria (22), 3) active disease (SELENA–SLEDAI score ≥6) at screening (18), and 4) seropositivity as defined by 2 positive ANA or anti-dsDNA test results (ANA titer ≥1:80 and/or anti-dsDNA antibody level ≥30 IU/ml), of which ≥1 test result had to be obtained during screening. The study entry criteria were identical to those in BLISS-52 (17). BLISS-76 enrolled patients from Europe and North/Central America (136 centers in 19 countries). A stable treatment regimen was required for ≥30 days before the first study dose; stable treatment could include prednisone (or equivalent) alone (7.5–40 mg/day) or combined (0–40 mg/day) with antimalarial drugs, nonsteroidal antiinflammatory drugs, and/or immunosuppressive therapies.

Exclusion criteria included serious intercurrent illness, severe active lupus nephritis, severe central nervous system manifestations, and pregnancy. Prior treatment with a B cell–targeted agent was exclusionary, as was any investigational biologic agent within 1 year of screening or an investigational nonbiologic agent within 60 days. Additional medication exclusions included IV cyclophosphamide within 6 months of screening; a tumor necrosis factor inhibitor, anakinra, IVIG, prednisone >100 mg/day, or plasmapheresis within 3 months of screening; and immunization with a live vaccine within 1 month of screening.

Each site was required to obtain ethics committee/institutional review board approval of the final study protocol. Patients' rights, safety, and well-being were protected based on the principles of the Declaration of Helsinki. Informed consent was obtained from each patient prior to study screening. The first patient was randomized in February 2007, and followup of the last patient was completed in March 2010.

Table 1. Baseline demographic and clinical characteristics of the treated patients*

Characteristic	Placebo (n = 275)	Belimumab 1 mg/kg (n = 271)	Belimumab 10 mg/kg (n = 273)
Female, no. (%)	252 (91.6)	253 (93.4)	259 (94.9)
Race, no. (%)†			
Indigenous American‡	36 (13.1)	33 (12.2)	34 (12.5)
White/Caucasian	188 (68.4)	192 (70.8)	189 (69.2)
Black/African American	39 (14.2)	40 (14.8)	39 (14.3)
Asian	11 (4.0)	6 (2.2)	11 (4.0)
Hispanic or Latino origin, no. (%)§	55 (20.0)	62 (22.9)	56 (20.5)
Age, years	40.0 ± 11.9	40.0 ± 11.4	40.5 ± 11.1
SLE disease activity			
Disease duration, years	7.4 ± 6.7	7.9 ± 7.1	7.2 ± 7.5
SELENA–SLEDAI score	9.8 ± 4.0	9.7 ± 3.7	9.5 ± 3.6
SELENA–SLEDAI score ≥10, no. (%)	140 (50.9)	144 (53.1)	136 (49.8)
≥1 BILAG A or 2 BILAG B scores, no. (%)	187 (68.0)	173 (63.8)	160 (58.6)
PGA score (0–3 VAS)	1.5 ± 0.5	1.4 ± 0.5	1.4 ± 0.5
Organ involvement			
BILAG A/B organ domain scores at baseline, no. (%)			
Musculoskeletal	195 (70.9)	177 (65.3)	179 (65.6)
Mucocutaneous	178 (64.7)	159 (58.7)	141 (51.6)
Hematologic	35 (12.7)	40 (14.8)	35 (12.8)
General	38 (13.8)	30 (11.1)	38 (13.9)
Vasculitis	30 (10.9)	23 (8.5)	18 (6.6)
Renal	21 (7.6)	14 (5.2)	24 (8.8)
Cardiovascular/respiratory	9 (3.3)	13 (4.8)	15 (5.5)
Neurologic	6 (2.2)	7 (2.6)	7 (2.6)
SDI score	1.0 ± 1.5	1.0 ± 1.4	1.0 ± 1.4
Proteinuria, gm/24 hours	0.4 ± 0.8	0.3 ± 0.7	0.4 ± 0.7
Proteinuria ≥2 gm/24 hours, no. (%)	11 (4.0)	7 (2.6)	15 (5.5)
Medications			
Daily prednisone use, no. (%)	212 (77.1)	211 (77.9)	200 (73.3)
>7.5 mg/day at baseline, no. (%)	126 (45.8)	130 (48.0)	120 (44.0)
Prednisone, mg/day	9.4 ± 8.9	8.7 ± 7.6	8.4 ± 7.9
Any immunosuppressant use, no. (%)¶	154 (56.0)	153 (56.5)	148 (54.2)
Mycophenolate mofetil	42 (15.2)	45 (16.6)	50 (18.3)
Azathioprine	57 (20.7)	52 (19.2)	58 (21.2)
Methotrexate	60 (21.9)	53 (19.6)	39 (14.3)
Antimalarial (aminoquinolone) use, no. (%)	180 (65.5)	171 (63.1)	168 (61.5)
Biomarkers			
BLyS above limit of detection (0.5 ng/ml), no. (%)#	269 (98.9)	268 (98.9)	263 (98.1)
ANA titer ≥1:80, no. (%)	253 (92.0)	256 (94.5)	245 (89.7)
Anti-dsDNA antibodies ≥30 IU/ml, no. (%)	174 (63.3)	171 (63.1)	179 (65.6)
Anti-dsDNA antibodies, IU/ml**	556 ± 931	451 ± 748	551 ± 911
C3, mg/liter	958 ± 303	995 ± 321	973 ± 325
C3 below LLN (90 mg/dl), no. (%)	116 (42)	100 (37)	115 (42)
C4, mg/dl	16 ± 9	17 ± 10	16 ± 10
C4 below LLN (16 mg/dl), no. (%)	143 (52)	141 (52)	147 (54)
IgG, gm/liter	16 ± 6	16 ± 7	15 ± 6
IgA, gm/liter	3.0 ± 1.5	2.9 ± 1.5	3.0 ± 1.5
IgM, gm/liter	1.1 ± 0.7	1.1 ± 0.7	1.2 ± 0.9
B cell subsets			
CD19+, /mm^3	137 ± 140	132 ± 188	134 ± 125
CD20+, /mm^3	136 ± 140	128 ± 187	131 ± 125
CD20–CD27^{bright} (short-lived plasma cells), /ml††	568 ± 770	473 ± 694	674 ± 1,009
T cell subsets			
CD3+, $\times 10^9$/liter	0.80 ± 0.48	0.78 ± 0.44	0.82 ± 0.50
CD3+CD4+, $\times 10^9$/liter	0.48 ± 0.33	0.48 ± 0.31	0.49 ± 0.35
CD3+CD8+, $\times 10^9$/liter	0.31 ± 0.24	0.30 ± 0.19	0.33 ± 0.22

* Except where indicated otherwise, values are the mean ± SD. SLE = systemic lupus erythematosus; SELENA–SLEDAI = Safety of Estrogens in Lupus Erythematosus National Assessment version of the SLE Disease Activity Index; BILAG = British Isles Lupus Assessment Group; PGA = physician's global assessment of disease activity; VAS = visual analog scale; SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; BLyS = B lymphocyte stimulator; ANA = antinuclear antibody; anti-dsDNA = anti–double-stranded DNA; LLN = lower limit of normal.
† Patients could be categorized in more than 1 race subgroup.
‡ Alaska Native or American Indian from North/South/Central America.
§ Also accounted for in the race subgroups.
¶ Excluding aminoquinoline antimalarials (hydroxychloroquine, chloroquine, quinacrine).
# Serum levels only determined prior to belimumab dosing because interference from belimumab precluded an accurate measurement of BLyS levels.
** In patients who were positive at baseline according to anti-dsDNA (IgG) assay with a detectable range of 30–3,600 IU/ml.
†† Rare subset count per ml = (rare cell event count)/(CD19+ event count) × CD19+ count per mm^3 × 1,000.

Randomization. With the exception of unblinded site pharmacists or designees whose responsibilities were restricted solely to receiving, preparing, and dispensing the study agent, all study site personnel and patients, as well as sponsor and clinical research organization personnel, were blinded to trial agent assignments. Separate study monitors were responsible for the blinded (clinical) and unblinded (study agent preparation) components of the trial. After screening, eligible

patients were randomly assigned via a centralized interactive voice response system to 1 of 3 treatment groups in a 1:1:1 ratio. At randomization, patients were stratified by screening SELENA–SLEDAI score (6–9 versus ≥10), proteinuria (<2 gm/24 hours versus ≥2 gm/24 hours), and race (African or indigenous American descent versus other).

Efficacy measures. The primary efficacy end point was the SRI response rate at week 52. An SRI response was defined as a ≥4-point reduction in SELENA–SLEDAI score, no new BILAG A organ domain score and no more than 1 new BILAG B score (19,20), and no worsening (increase <0.3) in physician's global assessment score versus baseline (18). Major secondary end points were SRI response rate at week 76, percentage of patients with a ≥4-point reduction from baseline in SELENA–SLEDAI score at week 52, change in physician's global assessment score at week 24, change in Short Form 36 version 2 (SF-36v2) health survey (23) physical component summary (PCS) score at week 24, and percentage of patients with a mean prednisone dose that was decreased ≥25% from baseline and was ≤7.5 mg/day during weeks 40–52. Disease activity was also assessed with the SLE Flare Index (21), modified to exclude the single criterion of increased SELENA–SLEDAI score to >12 as defining severe flare (18).

Biologic markers. Assessed biologic markers included serum Ig, complement (C3 and C4), autoantibodies (e.g., anti-dsDNA antibodies and ANAs), and B and T cell subsets. Serologic assessments were performed using enzyme-linked immunosorbent assay, except for ANAs, which were determined by indirect immunofluorescence on HEp-2 cells (Quest Diagnostics). Peripheral blood lymphocytes were collected at baseline and at weeks 8, 24, 52, and 76, forwarded to a central fluorescence-activated cell sorting facility (Nichols Laboratory), and stained with antibodies to quantitate B cells and B cell subsets as well as T cells and T cell subsets (CD3, CD4, and CD8).

Safety. AEs were coded according to the Medical Dictionary for Regulatory Activities version 12.0 preferred term or system organ class and were graded for severity using the Adverse Event Severity Grading Tables, modified from the National Institute of Allergy and Infectious Diseases Division of Microbiology and Infectious Diseases Adult Toxicity Tables (24).

Statistical analysis. The primary efficacy end point compared SRI response rates at week 52 between each belimumab treatment group and the placebo group using a logistic regression model adjusted for baseline randomization stratification factors. Patients who withdrew from the study or had changes in concomitant medications that were restricted by the protocol were considered treatment failures. Analysis was performed in a modified intent-to-treat population, which was defined as all randomized patients who received ≥1 dose of study agent. The target sample size of 810 patients (270 per group) was based on providing ≥90% power at the 5% significance level to detect ≥14% absolute improvement in SRI response rate at week 52 for 10 mg/kg belimumab relative to placebo. The primary efficacy analyses used a step-down procedure to control for the overall Type I error (2-sided $\alpha = 0.05$), comparing 10 mg/kg belimumab with placebo and then 1 mg/kg belimumab with placebo if 10 mg/kg was superior. Four sensitivity analyses of the primary end point at week 52 were prespecified in the protocol and analysis plan, including an unadjusted analysis, last observation carried forward (LOCF) analysis, completer analysis, and per-protocol analysis (which excluded patients with major protocol violations). For secondary end points, analyses of categorical variables were performed using a logistic regression model. Analysis of covariance was used for continuous variables, such as physician's global assessment score changes from baseline to week 24. The analyses were adjusted for baseline stratification factors.

RESULTS

Patient disposition and demographics. Of 1,353 patients screened, 826 were randomized, and 819 received ≥1 dose of study treatment (Figure 1). Baseline demographics, SLE disease characteristics, and medications were generally well balanced across treatment groups (Table 1). There were no differences among groups in discontinuation rates. Withdrawal rates in the placebo, 1 mg/kg belimumab, and 10 mg/kg belimumab groups were 25.5%, 20.3%, and 23.4%, respectively, at week 52, and 32.4%, 26.6%, and 30.0%, respectively, at week 76; reasons for discontinuation were similar across groups.

Primary efficacy end point: SRI response at week 52. There were more SRI responders at week 52 in the 10 mg/kg belimumab group than in the placebo group (43.2% versus 33.5%; $P = 0.017$) (Table 2 and Figure 2A). The percentage of SRI responders in the 1 mg/kg belimumab group (40.6%) was also numerically greater than that in the placebo group ($P = 0.089$). Consistent with the primary analysis, the 4 prespecified sensitivity analyses were also statistically significant with 10 mg/kg belimumab, but not with 1 mg/kg belimumab. The duration of SRI response in week 52 responders was significantly greater with 10 mg/kg belimumab than with placebo for 1–6 months before or after the week 52 visit (Figure 2B). Compared with patients treated with placebo, more patients treated with 10 mg/kg belimumab met the criterion for the SELENA–SLEDAI component of the SRI ($P = 0.006$). Belimumab at 1 mg/kg was associated with a greater likelihood of patients meeting the no-worsening criteria for the BILAG ($P = 0.013$) and physician's global assessment ($P = 0.012$) components of the SRI.

Major secondary efficacy end points. *SRI response at week 76.* The SRI response rates were numerically greater with 10 mg/kg belimumab (38.5%) ($P = 0.13$) and 1 mg/kg belimumab (39.1%) ($P = 0.11$) than with placebo (32.4%) at week 76 (Table 2 and Figure 2A).

Table 2. Clinical and biomarker outcomes*

Efficacy parameter	Placebo (n = 275)	Belimumab 1 mg/kg (n = 271)	Belimumab 10 mg/kg (n = 273)
SRI response rate at week 52†	92 (33.5)	110 (40.6)	118 (43.2)‡
≥4-point reduction in SELENA–SLEDAI score§	97 (35.3)	116 (42.8)	127 (46.5)¶
No worsening by BILAG#	180 (65.5)	203 (74.9)‡	189 (69.2)
No worsening by PGA	173 (62.9)	197 (72.7)‡	190 (69.6)
SRI modified by SELENA–SLEDAI score reduction at week 52			
≥5-point reduction**	56 (20.4)	84 (31.0)¶	89 (32.6)††
≥6-point reduction**	52 (18.9)	78 (28.8)¶	84 (30.8)¶
≥7-point reduction‡‡	29/216 (13.4)	42/217 (19.4)	46/216 (21.3)‡
≥8-point reduction‡‡	28/210 (13.3)	39/211 (18.5)	45/210 (21.4)‡
≥9-point reduction‡‡	12/147 (8.2)	21/150 (14.0)	22/143 (15.4)
≥10-point reduction‡‡	12/140 (8.6)	20/144 (13.9)	21/136 (15.4)
SRI response rate at week 76†§	89 (32.4)	106 (39.1)	105 (38.5)
≥4-point reduction in SELENA–SLEDAI score§	93 (33.8)	114 (42.1)‡	113 (41.4)
No worsening by BILAG#	162 (58.9)	187 (69.0)‡	173 (63.4)
No worsening by PGA	160 (58.2)	178 (65.7)	172 (63.0)
SRI modified by SELENA–SLEDAI score reduction at week 76			
≥5-point reduction**	60 (21.8)	77 (28.4)	84 (30.8)‡
≥6-point reduction**	56 (20.4)	73 (26.9)	79 (28.9)‡
≥7-point reduction‡‡	30/216 (13.9)	47/217 (21.7)‡	47/216 (21.8)‡
≥8-point reduction‡‡	27/210 (12.9)	42/211 (19.9)‡	46/210 (21.9)¶
≥9-point reduction‡‡	7/147 (4.8)	22/150 (14.7)¶	22/143 (15.4)¶
≥10-point reduction‡‡	7/140 (5.0)	21/144 (14.6)¶	19/136 (14.0)‡
Corticosteroid-sparing activity			
Prednisone reduced by ≥25% to ≤7.5 mg/day during weeks 40–52§	16/126 (12.7)	25/130 (19.2)	21/120 (17.5)
Prednisone reduced by ≥25% to ≤7.5 mg/day during weeks 64–76	22/126 (17.5)	35/130 (26.9)	29/120 (24.2)
Severe flares according to the SLE Flare Index			
Patients with flare over 76 weeks§§	73 (26.5)	50 (18.5)‡	56 (20.5)
Patients with flare from weeks 24 to 76¶¶	52/239 (21.8)	31/245 (12.7)¶	37/236 (15.7)
Biologic markers			
Normalization of low C3 (<90 mg/dl)			
Week 52	16/77 (20.8)	24/74 (32.4)	37/85 (43.5)¶
Week 76	13/70 (18.6)	19/70 (27.1)	40/78 (51.3)††
Normalization of low C4 (<16 mg/dl)			
Week 52	17/99 (17.2)	35/105 (33.3)¶	52/112 (46.4)††
Week 76	17/93 (18.3)	36/98 (36.7)¶	52/102 (51.0)††
Anti-dsDNA positive to negative##			
Week 52	10 (8.3)	23 (17.0)‡	19 (14.5)
Week 76	11 (9.8)	31 (24.8)¶	23 (19.2)‡

* Values are the number (%) or the number/total number (%) of patients. SRI = SLE Responder Index (see Table 1 for other definitions).
† Percentage of patients with a ≥4-point reduction in SELENA–SLEDAI score, no new BILAG A organ domain flare and no more than 1 new BILAG B flare, and no worsening in physician's global assessment score versus baseline (<0.3-point increase).
‡ $P < 0.05$ versus placebo.
§ Major secondary end point.
¶ $P < 0.01$ versus placebo.
# No new BILAG 1A/2B flares.
** SRI modified based on 5–6-point reduction in SELENA–SLEDAI score included all patients for analysis.
†† $P < 0.001$ versus placebo.
‡‡ SRI modified based on 7–10-point score reduction in SELENA–SLEDAI included only patients who had ≥7–10-point score at baseline.
§§ Using the placebo group as the referent, the hazard ratio (HR) for the 1 mg/kg belimumab group was 0.66 (95% confidence interval [95% CI] 0.46–0.94), and the HR for the 10 mg/kg belimumab group was 0.77 (95% CI 0.54–1.09).
¶¶ Using the placebo group as the referent, the HR for the 1 mg/kg belimumab group was 0.55 (95% CI 0.35–0.86), and the HR for the 10 mg/kg belimumab group was 0.70 (95% CI 0.46–1.07).
In patients who were positive at baseline according to anti-dsDNA (IgG) assay with a detectable range of 30–3,600 IU/ml.

Post hoc sensitivity analysis with higher SELENA–SLEDAI score thresholds. We evaluated the effect of belimumab using a modified SRI that required higher thresholds for the SELENA–SLEDAI component (i.e., starting from a ≥5-point reduction to a ≥10-point reduction). These more stringent response criteria increased the differentiation of belimumab treatment from placebo at both weeks 52 and 76, with 10 mg/kg

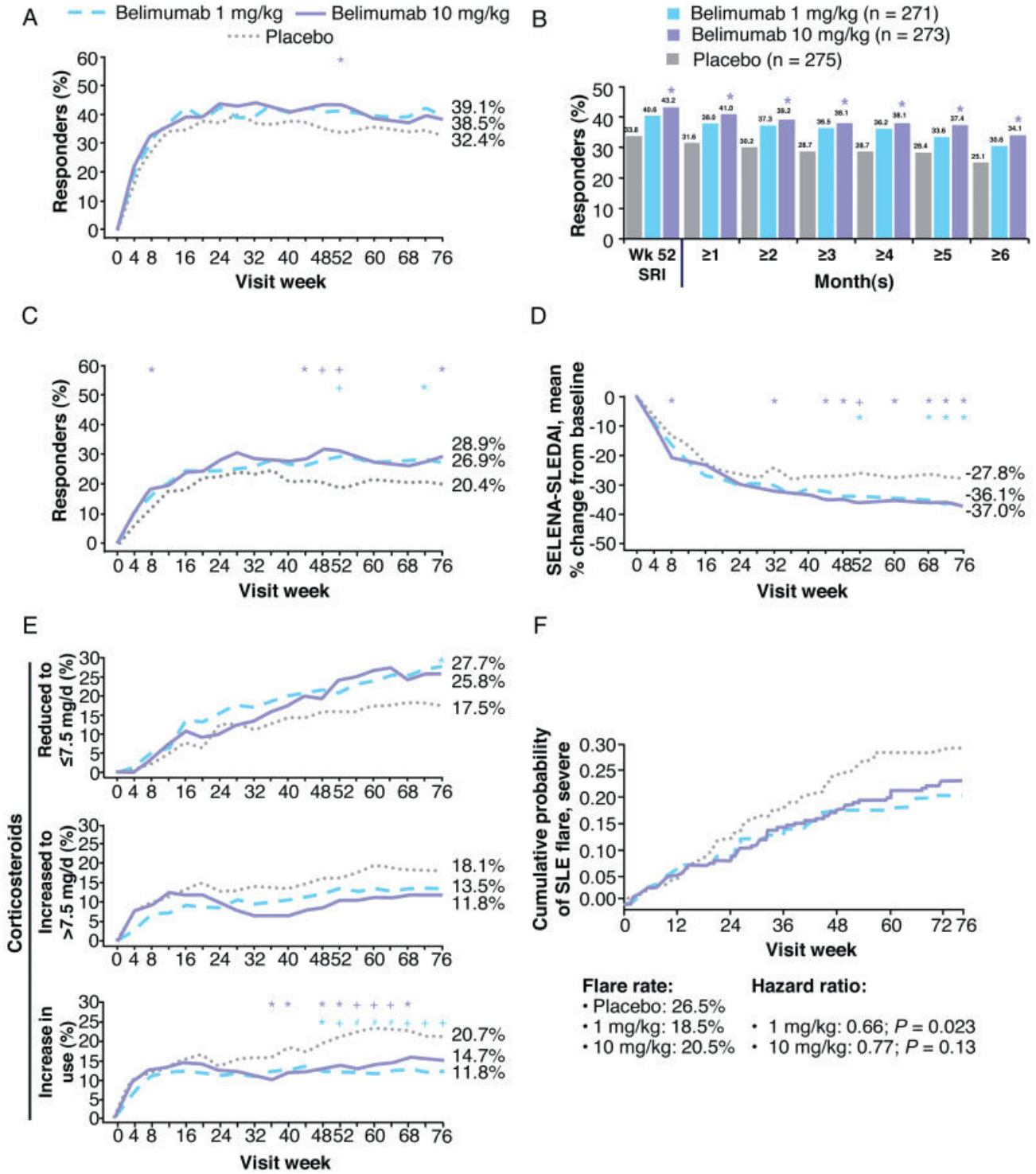

Figure 2. Select clinical outcomes. **A,** Systemic lupus erythematosus (SLE) Responder Index (SRI) response rate over 76 weeks. **B,** Durability of week 52 SRI response. Shown are SRI rates by number of consecutive months of response at any time between 1–6 months prior and 1–6 months after the week 52 response. **C,** Modified SRI response rate (based on ≥6-point reduction in the score on the Safety of Estrogens in Lupus Erythematosus National Assessment [SELENA] version of the SLE Disease Activity Index [SLEDAI]) over 76 weeks. **D,** Mean percent change from baseline in SELENA–SLEDAI score (last observation carried forward analysis). **E,** Percent of patients with corticosteroid dose reduced to ≤7.5 mg/day from >7.5 mg/day at baseline (n = 376) (top), with corticosteroid dose increased to >7.5 mg/day from ≤7.5 mg/day at baseline (n = 443) (middle), and with increased corticosteroid use over 76 weeks (bottom). **F,** Cumulative probability of severe SLE flare. ∗ = $P < 0.05$; + = $P < 0.01$; # = $P < 0.001$ (blue indicates 1 mg/kg belimumab versus placebo; magenta indicates 10 mg/kg belimumab versus placebo).

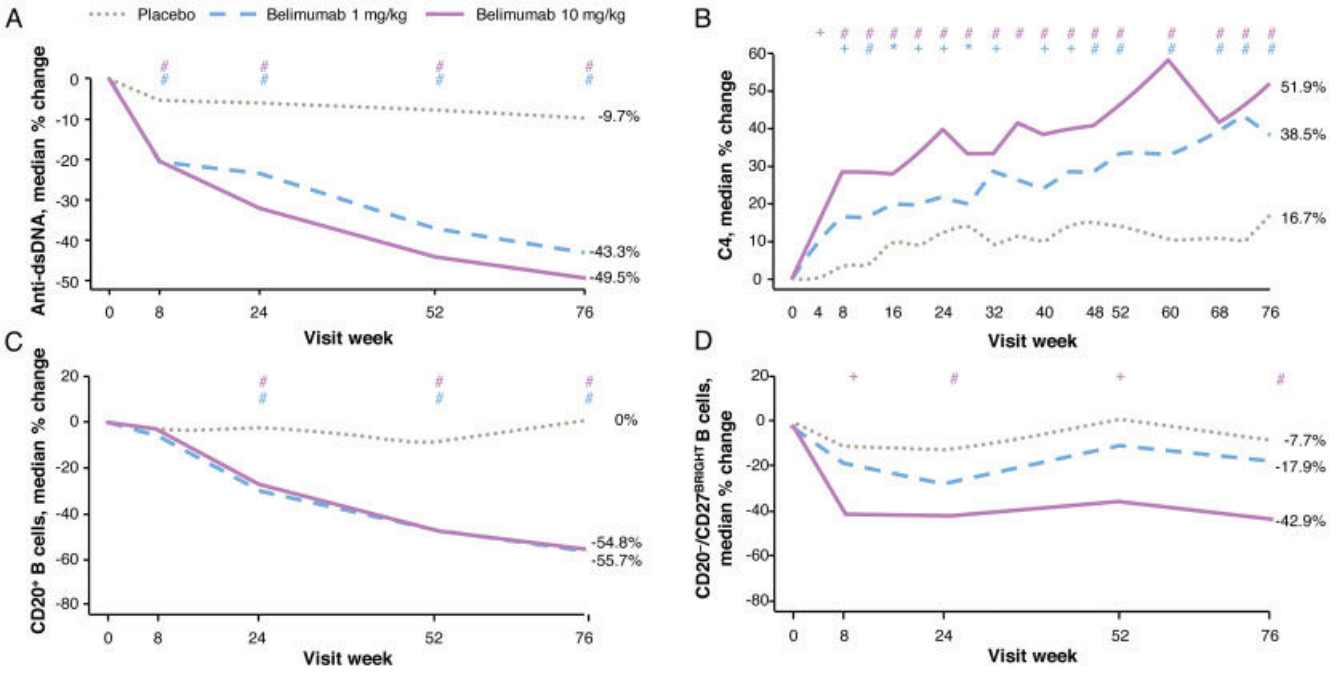

Figure 3. Select biomarker analyses. **A,** Median percent change in anti–double-stranded DNA (anti-dsDNA) levels in patients positive for anti-dsDNA at baseline. **B,** Median percent change in C4 in patients with low values (<16 mg/dl) at baseline. (At week 76, the median percent change values in C3 in patients with low values [<90 mg/dl] at baseline were 4.8%, 18.9%, and 21.1% for placebo, 1 mg/kg belimumab, and 10 mg/kg belimumab, respectively.) **C,** Median percent change in CD20+ B cell subset. **D,** Median percent change in CD20−CD27^{bright} short-lived plasma B cell subset. $* = P < 0.05$; $+ = P < 0.01$; $\# = P < 0.001$ (blue indicates 1 mg/kg belimumab versus placebo; magenta indicates 10 mg/kg belimumab versus placebo).

belimumab achieving a significant difference from placebo for every SELENA–SLEDAI threshold at week 76 (all $P < 0.05$) (Table 2 and Figure 2C).

SELENA–SLEDAI score reduction ≥4 points at week 52. Compared with patients receiving placebo, significantly more patients receiving 10 mg/kg belimumab had a ≥4-point reduction in SELENA–SLEDAI score at week 52 (46.5% versus 35.3%; $P = 0.006$) (Table 2). Evaluating SELENA–SLEDAI score changes (supporting analysis) using the LOCF imputation method revealed significant improvements in mean percent change in SELENA–SLEDAI score for 10 mg/kg belimumab from weeks 44 through 76 and for 1 mg/kg belimumab from weeks 52 through 76 (except at week 60) (Figure 2D).

Change in physician's global assessment score at week 24. There were no significant differences in mean change in physician's global assessment score at week 24 between the placebo (−0.49) and belimumab (−0.47 for 1 mg/kg and −0.44 for 10 mg/kg) groups.

Corticosteroid dose reduction between weeks 40 and 52. A subgroup of 376 patients (46%) was receiving >7.5 mg/day prednisone (or equivalent) at baseline. Greater proportions of patients receiving 1 mg/kg belimumab (19%) and 10 mg/kg belimumab (18%) were able to reduce corticosteroids by ≥25% and to ≤7.5 mg/day between weeks 40 and 52 compared with patients receiving placebo (13%), but these differences were not statistically significant (Table 2). Between weeks 64 and 76, a similar proportional prednisone reduction was observed. More patients treated with belimumab who were receiving >7.5 mg/day prednisone at baseline were able to lower their dose to ≤7.5 mg/day over time through week 76 (Figure 2E). In addition, fewer patients receiving belimumab required prednisone dose increases to >7.5 mg/day over 76 weeks, although the differences in these subgroups did not achieve statistical significance (Figure 2E).

Corticosteroid usage. There was a greater incidence of treatment failures at week 76 for violating prednisone dosing rules in the placebo group (14.9%) than in the 1 mg/kg belimumab (7.5%) ($P = 0.005$) and 10 mg/kg belimumab (8.1%) ($P = 0.011$) groups. There was also a trend toward a greater proportion of patients treated with placebo increasing their prednisone dose during most of the trial, including weeks 52–76 (Figure 2E).

Change in SF-36v2 score at week 24. There were no significant differences in mean change in SF-36v2

PCS score at week 24 between the belimumab groups (+3.78 for 1 mg/kg and +3.21 for 10 mg/kg) and the placebo group (+3.35). SF-36v2 PCS score improvements at week 52 were +4.37 ($P = 0.012$) for 1 mg/kg belimumab and +3.44 for 10 mg/kg belimumab versus +2.85 for placebo; at week 76, these improvements were +4.26 and +3.95 versus +3.37, respectively.

Supporting secondary efficacy analyses. *Reduction in risk of severe flare over 76 weeks based on the modified SLE Flare Index*. The risks of severe flares over 76 weeks were reduced by 34% with 1 mg/kg belimumab ($P = 0.023$) and by 23% with 10 mg/kg belimumab ($P = 0.13$) (Table 2 and Figure 2F). The magnitude of reduction in the risk of severe flares was even greater with belimumab treatment from weeks 24 to 76 (Table 2).

Biologic marker findings. Belimumab treatment produced rapid and sustained reductions in anti-dsDNA antibody levels, as well as increases in C3 and C4 concentrations, compared with placebo (Figures 3A and B). Normalization of low C3 and C4 and reversal of anti-dsDNA positivity were more likely with 10 mg/kg belimumab than with placebo (Table 2). Of patients with baseline anti-dsDNA values of 30–99 IU/ml, treatment with placebo, 1 mg/kg belimumab, and 10 mg/kg belimumab resulted in normalization at week 52 in 26%, 48%, and 40%, respectively; the corresponding rates for patients with baseline values >99 IU/ml were 1.1%, 2.2%, and 2.3%. Patients without anti-dsDNA antibodies at baseline converted to positive at week 52 at rates of 9.1%, 4.0%, and 1.4% in the placebo, 1 mg/kg belimumab, and 10 mg/kg belimumab groups, respectively.

Both doses of belimumab were associated with reductions in B cells (CD20+) at weeks 24, 52, and 76 ($P < 0.001$) (Figure 3C). These reductions were observed in several B cell subsets, including activated (CD20+ CD69+) and naive (CD20+CD27− [data not shown]) cells, similar in pattern to CD20+ B cells. Plasma cell subsets, including SLE-specific subsets ($CD19+CD27^{bright}$ $CD38^{bright}$ [data not shown]) similar to the short-lived plasma cell subset ($CD20-CD27^{bright}$) (Figure 3D), were significantly lower after treatment with 10 mg/kg belimumab than with placebo. Similar to the results seen in the phase II trial of belimumab (14,25), no changes in T cells (CD3+CD4+ and CD3+CD8+) or memory B cells (CD20+CD27+) occurred in any group at week 52 or 76 (data not shown).

Safety and tolerability. The incidence of AEs, laboratory abnormalities, and infections, as well as serious and/or severe AEs, including infections, malignancies, and deaths, was similar across groups (Table 3). Three deaths occurred in patients receiving belimumab (2 in the 1 mg/kg group and 1 in the 10 mg/kg group) during the study. One death was due to unknown causes, 1 to ovarian cancer, and 1 to cardiac arrest after the onset of a multiorgan severe SLE flare (in the 10 mg/kg group). None of the deaths were considered related to study treatment. Depression was reported more frequently with belimumab (6–7%) than with placebo (4%). There were no suicides or suicide attempts in any treatment group during this study. Seven patients ages 52–65 years were diagnosed as having malignancies, including 1 receiving placebo (carcinoid tumor of the stomach), 4 receiving 1 mg/kg belimumab (carcinoma of the cervix, breast cancer, ovarian cancer, and squamous cell carcinoma of the skin), and 2 receiving 10 mg/kg belimumab (basal cell carcinoma and squamous cell carcinoma of the skin).

Rates of serious or severe infection were similar in all treatment groups. No patients died of an infection. One opportunistic infection—disseminated cytomegalovirus infection—occurred in a patient 3 weeks after the third dose of 10 mg/kg belimumab and resolved with antiviral medication. This patient had a history of high-dose steroid use and was also being treated with azathioprine.

Infusion reactions (including hypersensitivity) were more common with belimumab than with placebo (14–16% versus 10%), with no apparent dose relationship. The rates of serious and/or severe infusion reactions were 0.7%, 0.7%, and 1.5% with placebo, 1 mg/kg belimumab, and 10 mg/kg belimumab, respectively, and no anaphylaxis was reported. There was a decrease in the incidence of infusion reactions after the second or third study dose. Hypersensitivity reactions on the day of an infusion occurred in 4 patients receiving 1 mg/kg belimumab; 2 were allergic reactions attributed to products or medications other than study medication, and 2 were cases of angioedema (one of which was considered related to belimumab). All infusion and hypersensitivity reactions resolved with antihistamine and/or prednisone treatment on the day of infusion.

In patients receiving placebo, 1 mg/kg belimumab, and 10 mg/kg belimumab, respectively, the proportions with shifts in immunoglobulin levels from high or normal at baseline to low by week 52 were as follows: 3.0%, 6.0%, and 9.7% for IgG; 0.7%, 1.9%, and 4.5% for IgA; and 7.4%, 20.8%, and 20.9% for IgM. One patient in each treatment group had a grade 3 IgG reduction, which was not associated with infection.

Five pregnancies occurred during the study in patients who received belimumab (3 receiving 1 mg/kg and 2 receiving 10 mg/kg). Three pregnancies resulted in

Table 3. Treatment-emergent AEs and pregnancy outcomes during 76 weeks of study*

	Placebo (n = 275)	Belimumab 1 mg/kg (n = 271)	Belimumab 10 mg/kg (n = 273)
Treatment-emergent AEs			
≥1	253 (92.0)	253 (93.4)	253 (92.7)
≥1 serious	54 (19.6)	63 (23.2)	61 (22.3)
≥1 severe	52 (18.9)	51 (18.8)	54 (19.8)
Discontinuations due to AEs	23 (8.4)	18 (6.6)	23 (8.4)
Deaths	0	2 (0.7)	1 (0.4)
Malignant neoplasms			
All	1 (0.4)	4 (1.5)	2 (0.7)
Solid organ†	1 (0.4)	3 (1.1)	1 (0.4)
Nonmelanoma skin‡	0	1 (0.4)	1 (0.4)
Infections			
All	190 (69.1)	202 (74.5)	202 (74.0)
≥1 serious infection AE	16 (5.8)	19 (7.0)	20 (7.3)
≥1 severe infection AE§	11 (4.0)	8 (3.0)	7 (2.6)
Opportunistic infection	0	0	1 (0.4)
Treatment-emergent AEs in ≥10% of any treatment group			
Upper respiratory tract infection	58 (21.1)	53 (19.6)	54 (19.8)
Headache	38 (13.8)	56 (20.7)	44 (16.1)
Urinary tract infection	43 (15.6)	50 (18.5)	44 (16.1)
Arthralgia	43 (15.6)	43 (15.9)	41 (15.0)
Nausea	27 (9.8)	43 (15.9)	46 (16.8)
Diarrhea	28 (10.2)	35 (12.9)	33 (12.1)
Nasopharyngitis	24 (8.7)	29 (10.7)	43 (15.8)
Sinusitis	28 (10.2)	21 (7.7)	31 (11.4)
Back pain	21 (7.6)	26 (9.6)	27 (9.9)
Fatigue	25 (9.1)	27 (10.0)	21 (7.7)
Pyrexia	21 (7.6)	23 (8.5)	29 (10.6)
Bronchitis	21 (7.6)	19 (7.0)	32 (11.7)
Insomnia	13 (4.7)	27 (10.0)	17 (6.2)
Infusion reactions¶			
All (including hypersensitivity)	27 (9.8)	42 (15.5)	37 (13.6)
Requiring medical intervention#	9 (3.3)	16 (5.9)	17 (6.2)
Severe	1 (0.4)	1 (0.4)	3 (1.1)
Laboratory abnormalities of grade 3 or 4 in >2% of patients			
WBC count $<2 \times 10^9$/liter	12 (4.4)	11 (4.1)	11 (4.0)
Neutrophil count $<1 \times 10^9$/liter	20 (7.3)	18 (6.7)	16 (5.9)
Lymphocyte count $<5 \times 10^8$/liter	80 (29.1)	78 (29.2)	76 (27.9)
Hemoglobin ≤80 gm/liter	15 (5.5)	7 (2.6)	5 (1.8)
Prothrombin time**	31 (11.6)	36 (13.6)	30 (11.2)
Proteinuria (>2 gm/24 hours)††	21 (7.7)	19 (7.1)	28 (10.4)
Hypogammaglobulinemia (<4 gm/liter)‡‡	1 (0.4)	1 (0.4)	1 (0.4)
Median percent change in Ig from baseline at week 76§§			
IgG	−0.8	−15.1	−16.4
IgA	−2.1	−18.0	−20.4
IgM	−3.8	−31.8	−35.0
Pregnancy			
All	0	3	2
Live birth without congenital anomaly	0	2¶¶	1##

* Except where indicated otherwise, values are the number (%) of patients who experienced an adverse event (AE) or had an abnormal laboratory test result over 76 weeks of study. WBC = white blood cell.
† One carcinoid stomach tumor in the placebo group; one stage 0 cervix carcinoma, one breast cancer, and one ovarian cancer in the 1 mg/kg belimumab group; and one basal cell carcinoma in the 10 mg/kg belimumab group.
‡ Squamous cell carcinoma.
§ Grade 3 or 4.
¶ Infusion reactions that occurred on the day of infusion and resolved within 7 days, and all hypersensitivity reactions that occurred on the day of infusion.
# Study agent interrupted or discontinued, or drug given.
** Normal = 9–11.5 seconds, grade 3 = >1.5–3.0 × upper limit of normal (ULN), grade 4 = >3.0 × ULN. Eighty-one percent, 81%, and 87% of patients receiving placebo, 1 mg/kg belimumab, and 10 mg/kg belimumab, respectively, with grade 3/4 prothrombin time were receiving warfarin or other vitamin K antagonists.
†† Spot urine protein:creatinine ratio (mg:mg) was converted to gm/24 hours.
‡‡ Grade 3 = IgG <4 gm/liter.
§§ Determined at weeks 8, 16, 24, 32, 40, 52, 64, and 76.
¶¶ The third outcome was an elective termination.
The second pregnancy was lost to followup.

normal live births and 1 in elective termination, and 1 patient was lost to followup.

DISCUSSION

This randomized clinical trial of patients with a broad range of active SLE manifestations met its primary efficacy end point by demonstrating a reduction in SLE disease activity with 10 mg/kg belimumab added to standard therapy without worsening of patients' overall conditions or the development of significant disease activity in new organ systems. All 4 sensitivity analyses of the primary end point were statistically significant for 10 mg/kg belimumab at week 52; however, none were significant for 1 mg/kg belimumab, although the SRI response rate with that dose was numerically greater than that achieved with standard therapy alone. These results are consistent with those from the recently reported BLISS-52 trial, although the effect size in BLISS-52 was greater (17). The 2 studies evaluated the same biologic agent with similar patient entry criteria, but they were performed in different regions of the world with differences in available and accepted SLE therapies. Taken together, they provide compelling evidence of the efficacy of belimumab in patients with active, autoantibody-positive SLE.

The SRI response rates were numerically higher with belimumab than with placebo at week 76, but the differences were not statistically significant. The trial was designed and powered to evaluate response rates at week 52. It is likely that the ability to discriminate between doses was compromised at week 76 because of an additional 7% dropout rate that occurred in each group between weeks 52 (23%) and 76 (30%). In addition, the more liberal use of prednisone in the placebo group over 76 weeks could have reduced disease activity more than in the belimumab groups. Durability of the benefit of belimumab in reducing SLE disease activity, however, was supported by several findings in the study. For patients with a week 52 SRI response, a greater percentage receiving 10 mg/kg belimumab than standard therapy alone had a durable response lasting 1–6 months before or after week 52. Incorporating more stringent thresholds (5–10 points) of SELENA–SLEDAI score reduction into the SRI revealed that these modified SRI response rates were even more differentiated in the belimumab treatment groups compared with those in the group receiving standard therapy alone at weeks 52 through 76. Improvements in the percent change from baseline in SELENA–SLEDAI score were observed with both belimumab doses at week 52 and persisted through week 76 compared with standard therapy alone. Trends toward greater reduction in severe flares (by the SLE Flare Index) were observed through week 76 with both belimumab doses compared with standard therapy. The reduction in severe flares and decreased steroid use observed with belimumab may reduce long-term damage, potentially resulting in reduced disease costs and improved health-related quality of life (26–29). In fact, improvement in the SF-36v2 PCS score was observed at week 52 in patients treated with belimumab.

Belimumab treatment resulted in sustained improvements in serologic activity. Significant reductions in anti-dsDNA antibody titers and increases in C3 and C4 concentrations were observed with both belimumab doses at week 8 and persisted through week 76. The reductions in median anti-dsDNA IgG antibody levels (44–49%) with belimumab were greater than the reductions in total IgG (15–16%), suggesting a selective effect on autoantibody-producing cells (30,31). The significant reductions in B cell subsets observed with belimumab in this trial were similar to those noted in the phase II study (14,25). Reduction of BLyS-dependent activated B cells may decrease production of proinflammatory cytokines (32), while reduction of SLE-specific short-lived plasmablasts can reduce autoantibody production (25,30,31). In BLISS-76, reductions were observed in activated and naive B cells (both belimumab doses) and in short-lived plasma cells including SLE-specific plasma cells (10 mg/kg), but not in T cells (25) and memory B cells (14). By neutralizing BLyS, which is overexpressed in SLE and promotes B cell survival, belimumab may restore the ability of autoimmune B cells to undergo apoptosis in a partially selective manner and ultimately lead to reduced SLE disease activity (7,12).

Belimumab treatment was generally well tolerated, and AEs reported with both doses plus standard therapy were similar to those with standard therapy alone. Malignancies, occurring in 6 patients age >50 years who received belimumab, varied in the organ of origin. The rate of malignancies (excluding nonmelanoma skin cancers) per 100 patient-years in all patients with SLE treated with belimumab as of December 31, 2009 (odds ratio 0.45 [95% confidence interval 0.27–0.72]) is consistent with that reported in the literature for patients with SLE (odds ratio 0.53 [95% confidence interval 0.48–0.59]) (33,34). Infusion and hypersensitivity reactions, although more frequent with belimumab than with placebo, were uncommon, responded to standard medical management, and decreased after the first 3 infusions.

Until larger numbers of patients are treated with belimumab for longer durations, the incidence of rare,

severe, or serious AEs will remain unknown. It should also be noted that the BLISS-76 study design was not powered to compare risks against the background of different standard therapies, nor could some patient subpopulations be evaluated (e.g., pediatric patients, patients with severe active lupus nephritis, and those with severe active central nervous system involvement) since these groups were excluded from the trial.

In conclusion, this international phase III trial in patients with ANA- or anti-dsDNA–positive SLE treated with standard therapy plus belimumab or with standard therapy plus placebo met the 1-year SRI primary efficacy end point and provides supportive evidence of the durability of effect until 76 weeks.

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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 published. Dr. Furie 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. Furie, Petri, Zamani, Cervera, Wallace, Chatham, Ginzler, Zhong, Freimuth, van Vollenhoven.

Acquisition of data. Zamani, Cervera, Wallace, Tegzová, Sanchez-Guerrero, Schwarting, Merrill, Chatham, Stohl, Ginzler, Hough, Zhong, Freimuth, van Vollenhoven.

Analysis and interpretation of data. Furie, Petri, Zamani, Cervera, Wallace, Stohl, Ginzler, Hough, Zhong, Freimuth, van Vollenhoven.

ROLE OF THE STUDY SPONSORS

Human Genome Sciences was involved in the conception, design, implementation, and supervision of this study; data analysis and interpretation; statistical analysis; and manuscript drafting, revision, and approval. GlaxoSmithKline was involved in the design of this study and in manuscript drafting, revision, and approval. Both sponsors agreed to submit the manuscript for publication and approved the content of the manuscript. Publication of the manuscript was contingent on approval of all authors as well as that of the sponsors.

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