Long-Term Safety and Efficacy of Belimumab in Patients With Systemic Lupus Erythematosus

A Continuation of a Seventy-Six–Week Phase III Parent Study in the United States

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Objective. We undertook this US multicenter continuation study (GlaxoSmithKline study BEL112233; ClinicalTrials.gov identifier: NCT00724867) to assess long-term safety and efficacy of belimumab in patients with systemic lupus erythematosus (SLE) who completed the Study of Belimumab in Subjects with SLE 76-week trial (ClinicalTrials.gov identifier: NCT00410384).

Methods. Patients continued to receive the same belimumab dose plus standard therapy; patients previously receiving placebo received 10 mg/kg belimumab. The primary outcome measure was long-term safety of belimumab (frequency of adverse events [AEs] and damage assessed using the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index [SDI], evaluated every 48 weeks [1 study year]). Other assessments included the SLE Responder Index (SRI), flare rates (using the modified SLE Flare Index [SFI]), prednisone use, and B cell levels.

Results. Of 268 patients, 140 completed the study and 128 withdrew. The mean $\pm$ SD score on the Safety of Estrogens in Lupus Erythematosus National Assessment version of the SLE Disease Activity Index (SELENA–SLEDAI) at baseline was 7.8 $\pm$ 3.86. The mean $\pm$ SD SDI score increased by 0.4 $\pm$ 0.68 from its value at baseline (1.2 $\pm$ 1.51). The overall incidence of treatment-related and serious AEs remained stable or declined through study year 7. An SRI response was achieved by 41.9% and 75.6% of patients at the study year 1 and study year 7 midpoints, respectively. At the study year 7 midpoint, relative to baseline, 78.2% had achieved a $\geq$4-point reduction in the SELENA–SLEDAI score, 98.4% had no new British Isles Lupus Assessment Group (BILAG) A organ domain score and no more than 1 new BILAG B organ domain score, 93.7% had no worsening in the physician's global assessment of disease activity, 20.6% had experienced $\geq$1 severe SFI flare, the mean decrease in prednisone dose was 31.4%, and the median change in CD20+ B cell numbers was -83.2%.

Conclusion. These long-term exposure results confirm the previously observed safety and efficacy profiles of belimumab in patients with SLE.

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Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder that affects a number of organ systems (1) and causes a marked impairment in quality of life (QoL) (2,3). Active disease (4,5) and medication toxicities contribute to the accrual of long-term organ damage (6–8). Corticosteroids and immunosuppressant drugs have demonstrated clinical benefits (9); however, concerns remain about the safety of their long-term use (6–8).

Belimumab is a human IgG1λ monoclonal antibody licensed for the treatment of adult patients with

active, autoantibody-positive SLE who are receiving standard therapy. Belimumab binds to and inhibits the activity of soluble human B lymphocyte stimulator protein (10). A placebo-controlled phase II study showed that intravenous (IV) belimumab plus standard therapy was generally well tolerated (11); a good safety profile was maintained over 7 years (12). Two phase III studies, the Study of Belimumab in Subjects with SLE 52-week (BLISS-52) and 76-week (BLISS-76) trials, demonstrated the safety and efficacy of belimumab in patients with autoantibody-positive, active SLE (13,14). The long-term safety and efficacy of belimumab were examined in 2 open-label continuation studies (GlaxoSmithKline [GSK] studies BEL112233 and BEL112234) in patients who completed the BLISS studies. A pooled interim analysis of these 2 long-term continuation studies demonstrated low rates of organ damage accrual in patients with moderate-to-severe SLE, and safety over 5 years of exposure (15). Herein, we present the clinical results of the complete BLISS-76 continuation study BEL112233 conducted in US-only patients. Due to the study design, all non-US patients in BLISS-76 and BLISS-52 entered the rest-of-world continuation study BEL112234 (ClinicalTrials.gov identifier: NCT00712933).

The objectives of this continuation study were to provide continuing treatment to patients who completed BLISS-76 and evaluate the long-term safety and tolerability, impact on QoL, and efficacy of belimumab treatment in patients with SLE. The long-term impact of belimumab on QoL in patients with SLE will be reported separately.

PATIENTS AND METHODS

Study design. This was a multicenter, continuation study (GSK study BEL112233; ClinicalTrials.gov identifier: NCT00724867) conducted in patients who completed the 76-week phase III parent study BLISS-76 (GSK study BEL110751; ClinicalTrials.gov identifier: NCT00410384) in the US (14). In BLISS-76, patients were randomized to receive 1 mg/kg belimumab IV, 10 mg/kg belimumab IV, or placebo, plus standard therapy for 76 weeks (14). Patients who previously received placebo received 10 mg/kg belimumab in the continuation study. Patients randomized to receive belimumab continued to receive the same dose as in the parent study (1 or 10 mg/kg IV every 28 days) plus standard therapy. Following a protocol amendment (March 9, 2011), patients receiving 1 mg/kg belimumab had their dose increased to 10 mg/kg. Data on all patients receiving belimumab during this study were pooled for analysis.

To be eligible for enrollment, patients had to have completed BLISS-76 through week 72 and be able to receive the first dose of belimumab within 4 weeks (minimum 2 weeks, maximum 8 weeks). Patients were excluded if in the investigator's opinion they presented with clinical evidence of uncontrolled, acute, or chronic disease not due to SLE. Other key exclusion criteria included occurrence of an adverse event (AE) in the parent trial that would place the patient at undue risk, or laboratory abnormalities.

Since the study was designed to have 48-week study years, study years do not align with calendar years. The study was designed to end either after 5 calendar years from the date of enrollment of the last patient or when fewer than 100 patients remained in the trial, whichever occurred first. The study was conducted from August 5, 2008 to March 26, 2015, and up to 8 calendar years of data were collected (maximum exposure 2,908 days) (Figure 1).

Clinical site personnel remained blinded with regard to parent study treatment until results of the parent study were made public. The study was performed in accordance with the Declaration of Helsinki (16). All sites maintained ethics committee and institutional review board approval, and written informed consent was obtained from all patients.

Study end points. The primary objective of this study was the evaluation of the long-term safety of belimumab, as assessed by AEs, AEs of special interest, vital signs, and clinical laboratory tests (hematology, chemistry, routine urinalysis, and immunogenicity testing). Organ damage was assessed using the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) (17). Assessments were performed at week 24 (study year midpoint) and week 48 (study year end, referred to hereafter as study year). AEs were monitored throughout the study and for 8 weeks following the last dose of belimumab. Clinical laboratory assessments were performed on day 0, at weeks 4, 12, 24, 36, and 48 of study year 1, and at weeks 24 and 48 of each study year thereafter. Organ damage was assessed every 48 weeks.

Efficacy and biomarker assessments were exploratory. The primary efficacy assessment was the SLE Responder Index (SRI) (18) response rate, a validated composite end point defined as a ≥4-point reduction from baseline in the Safety of Estrogens in Lupus Erythematosus National Assessment version of the SLE Disease Activity Index (SELENA–SLEDAI) score (19), no worsening in the physician's global assessment of disease activity on a 0–10-cm visual analog scale (<0.3 points from baseline), and no new British Isles Lupus Assessment Group (BILAG) A or no more than 1 new BILAG B organ domain score (20).

Other efficacy assessments included the SELENA–SLEDAI, BILAG, physician's global assessment of disease activity, flare rates, prednisone use, and biomarkers. Flare rates were assessed by the SLE Flare Index (SFI) (19) and the BILAG. SFI flare rates (mild/moderate or severe) were defined by the modified SELENA–SLEDAI SFI (the modified SFI excludes severe flares that were triggered only by an increase in the SELENA–SLEDAI score to >12) (21). BILAG flare was defined by at least 1 new BILAG A organ domain score or >1 new BILAG B organ domain score compared with baseline (21). Biomarker assessments included anti–double-stranded DNA (anti-dsDNA) levels, serum complement levels, proteinuria values, serum Ig levels, and B cell subsets. Patients with a baseline SELENA–SLEDAI score of <4 at entry into the continuation study were excluded from the SRI analysis. Efficacy and biomarker assessments were performed every 24 weeks from the first dose of belimumab, with the exception of serum Ig levels, which were tested at week 24 and week 48 during study year 1 and then every 48 weeks. Concomitant corticosteroids were converted to a prednisone equivalent average daily dose (mg/day).
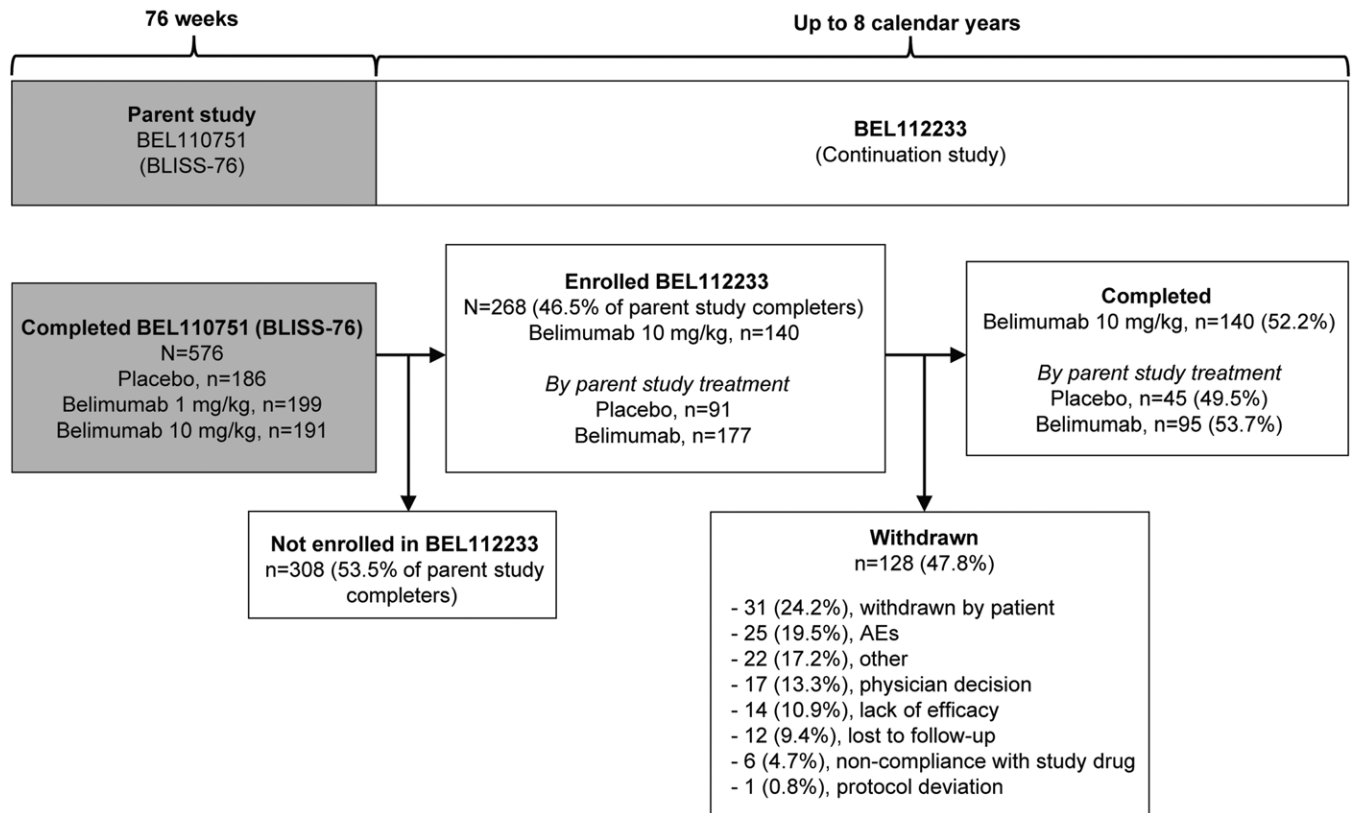
Figure 1. Disposition of the systemic lupus erythematosus (SLE) patients and enrollment by treatment in the Study of Belimumab in Subjects with SLE 76-week (BLISS-76) trial. This continuation study (GlaxoSmithKline [GSK] study BEL112233) was designed to end either after 5 calendar years from the date of enrollment of the last patient or when fewer than 100 patients remained in the trial, whichever occurred first. Patients at non-US sites were not eligible for enrollment into this study and had the opportunity to enroll in another open-label, long-term continuation study, GSK study BEL112234. For patients who received placebo in the parent study (BLISS-76; GSK study BEL110751), baseline was the last assessment prior to their first dose of belimumab, at the start of the continuation study. For patients who received belimumab in the parent study, baseline was the latest assessment prior to commencing the parent study. One patient who withdrew from the continuation study reported an adverse event (AE) leading to discontinuation, but the investigator-recorded reason for withdrawal was "physician decision."

Post hoc analyses were carried out for several parameters of interest. Baseline disease characteristics were examined for patients who withdrew and those who completed the study, to investigate completer bias. Withdrawals among SRI responders were reported, and severe flares were examined according to which severe SFI flare criteria were met. In addition, the proportions of patients who experienced normalization of anti-dsDNA and complement levels and who discontinued prednisone during the study were examined.

Statistical analysis. No formal statistical hypothesis testing was performed, and all analyses were descriptive and exploratory. Analyses included those patients enrolled in the continuation study who received at least 1 dose of belimumab. Patients who received 1 mg/kg or 10 mg/kg belimumab in the parent study were pooled for all analyses. Baseline was defined as the last assessment prior to the first dose of belimumab (day 0). Therefore, baseline for the parent study placebo group was the last assessment prior to their first dose of belimumab, at the start of the continuation study. For patients receiving active treatment in the parent study, baseline was the latest assessment prior to commencing the parent study, BLISS-76.

AEs from both the parent and continuation studies were coded according to the Medical Dictionary for Regulatory Activities, version 17.1. All AE data were summarized by study year according to the recorded start date of the AE. AEs that continued for >1 study year were reported in the year they first occurred; repeat AE episodes were reported in the year they reappeared. If the AE onset date was missing, it was assumed the start date was study year 1. If the AE end date was missing, it was assumed the AE continued until study end. AEs of special interest included malignant neoplasms, postinfusion systemic reactions, infections, depression, suicide, and self-injury. Continuous variables were summarized, reporting mean and SD, median and 25th and 75th percentile, and minimum and maximum. Categorical variables were summarized with frequency counts and percentages. All analyses were performed using SAS software, version 9.3.

RESULTS

Patient population. The modified intent-to-treat (ITT) population comprised 268 patients (46.5% of parent study completers; non-US patients in the parent study were not eligible for this study); 140 patients (52.2%) completed the continuation study, and 128 patients (47.8%) withdrew. The majority of patients were white (186 of 268 [69.4%]) and female (250 of 268 [93.3%]), with a mean ± SD age of 42.8 ± 11.33 years (Table 1). The duration of SLE ranged from 0 to 36 years, with a mean ± SD of 7.7 ± 6.77 years. The majority of patients (188 of 268 [70.1%]) entered the continuation study with a baseline SELENA–SLEDAI score of ≤9 and a mean ± SD SDI of 1.2 ± 1.51. The mean ± SD duration of belimumab exposure was 1,962.1 ± 746.44 days, with a median of 2,166.5 days (range 28–2,908).

The number of patients withdrawing from the study each year remained consistent throughout the study, and the number of patients starting each yearly interval declined at similar rates among patients initially treated with belimumab in the parent study and those treated with placebo (see Supplementary Figure 1, available on the *Arthritis & Rheumatology* web site at http://online library.wiley.com/doi/10.1002/art.40439/abstract). The 3 most common reasons for withdrawal were withdrawal by patient (31 of 128 [24.2%]), AE (25 of 128 [19.5%]), and other (22 of 128 [17.2%]) (Figure 1). A post hoc review of the data indicated that where a reason was provided for withdrawal by patient, the 2 requests most often cited were a desire to conceive and logistical reasons (data not shown). The majority of patients (11 of 14) who withdrew due to lack of efficacy did so in the first 4 years of the study. Disease flares were a commonly cited reason for withdrawal due to lack of efficacy (5 of 14 patients).

Baseline characteristics of patients who withdrew from the study and of those who completed were examined post hoc. The mean ± SD SELENA–SLEDAI scores at baseline were 7.8 ± 3.85 and 7.8 ± 3.89 among those who withdrew and those who completed, respectively. Thirty-eight of 128 patients (29.7%) who withdrew had a SELENA–SLEDAI score of ≥10 at baseline, compared with 42 of 140 patients (30.0%) who completed the study. Of patients who withdrew, 91 of 128 (71.1%) had a score of >1 on the physician's global assessment of disease activity, compared with 98 of 140 patients (70.0%) who completed the study. Among patients who withdrew, 63 of 128 (49.2%) had active disease at baseline, defined as ≥1 BILAG A or ≥2 BILAG B organ domain scores, while 74 of 140 patients (52.9%) who completed the study had active

Table 1. Baseline characteristics of the 268 patients*

Female	250 (93.3)
Age, mean ± SD years	42.8 ± 11.33
BMI, mean ± SD kg/m^2	28.4 ± 7.43
Race	
White	186 (69.4)
Black or African American/African heritage	57 (21.3)
Asian	13 (4.9)
SLE disease duration, mean ± SD years	7.7 ± 6.77
SELENA–SLEDAI score (0–105), mean ± SD	7.8 ± 3.86
SELENA–SLEDAI score	
≤9	188 (70.1)
≥10	80 (29.9)
Complement levels	
Low C3 and/or low C4	119 (44.4)
No low C3 or C4	149 (55.6)
PGA (0–10-cm VAS), mean ± SD	1.19 ± 0.60
SDI score (0–47), mean ± SD	1.2 ± 1.51
SLE Flare Index	
At least 1 flare	65 (24.3)
At least 1 severe flare	2 (0.7)
BILAG organ domain involvement†	137 (51.1)
Concomitant medications	
Corticosteroids only	21 (7.8)
Immunosuppressant drugs only	11 (4.1)
Antimalarials only	41 (15.3)
Average prednisone dose	
0 mg/day	95 (35.4)
>0 to ≤7.5 mg/day	87 (32.5)
>7.5 to ≤40 mg/day	86 (32.1)

* Except where indicated otherwise, values are the number (%). BMI = body mass index: SLE = systemic lupus erythematosus; SELENA–SLEDAI = Safety of Estrogens in Lupus Erythematosus National Assessment version of the SLE Disease Activity Index; PGA = physician's global assessment of disease activity; VAS = visual analog scale; SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.
† At least 1 new British Isles Lupus Assessment Group (BILAG) A organ domain score or >1 new BILAG B organ domain score compared with baseline.

disease at baseline. At baseline, ≥1 SFI flare had been experienced by 28 of 128 patients (21.9%) who then withdrew and by 37 of 140 patients (26.4%) who completed. Among patients who withdrew, 2 of 128 (1.6%) experienced ≥1 severe flare prior to baseline; no patients who completed the study had a severe flare prior to baseline. Twenty-three of 128 patients (18.0%) who withdrew from the study had proteinuria >0.5 gm/24 hours at baseline, compared with 13 of 140 (9.3%) who completed. Low C3/C4 levels (C3 <0.9 gm/liter and/or C4 <0.16 gm/liter) at baseline were reported in 52 of 128 patients (40.6%) who withdrew and 67 of 140 (47.9%) who completed. Overall, baseline disease characteristics between patients who withdrew and those who completed were similar.

Safety. *AEs.* At least 1 AE was experienced by 267 of 268 patients (99.6%), and 145 of 268 patients (54.1%) had an AE that was considered by the investigator to be drug-related (Table 2). Discontinuation of belimumab due to an AE occurred in 26 of 268

Table 2. Incidence of treatment-emergent AEs by study year*

	Any time postbaseline (n = 268)	Year 0–1 (n = 268)	Year 1–2 (n = 259)	Year 2–3 (n = 244)	Year 3–4 (n = 219)	Year 4–5 (n = 202)	Year 5–6 (n = 192)	Year 6–7 (n = 130)	Year 7+ (n = 65)
At least 1 AE	267 (99.6)	260 (97.0)	235 (90.7)	206 (84.4)	184 (84.0)	167 (82.7)	145 (75.5)	87 (66.9)	31 (47.7)
At least 1 treatment-related AE†	145 (54.1)	89 (33.2)	55 (21.2)	40 (16.4)	35 (16.0)	30 (14.9)	32 (16.7)	13 (10.0)	3 (4.6)
At least 1 serious AE	112 (41.8)	33 (12.3)	30 (11.6)	25 (10.2)	22 (10.0)	24 (11.9)	16 (8.3)	13 (10.0)	3 (4.6)
Serious AEs by system organ class‡									
Infections and infestations	44 (16.4)	13 (4.9)	9 (3.5)	4 (1.6)	6 (2.7)	8 (4.0)	7 (3.6)	2 (1.5)	1 (1.5)
Musculoskeletal and connective tissue	22 (8.2)	7 (2.6)	5 (1.9)	3 (1.2)	2 (0.9)	4 (2.0)	2 (1.0)	1 (0.8)	0
At least 1 severe AE	100 (37.3)	31 (11.6)	19 (7.3)	23 (9.4)	21 (9.6)	18 (8.9)	15 (7.8)	10 (7.7)	3 (4.6)
Severe AEs by system organ class‡									
Infections and infestations	28 (10.4)	7 (2.6)	2 (0.8)	4 (1.6)	7 (3.2)	6 (3.0)	3 (1.6)	0	1 (1.5)
Musculoskeletal and connective tissue	23 (8.6)	9 (3.4)	4 (1.5)	4 (1.6)	1 (0.5)	5 (2.5)	3 (1.6)	1 (0.8)	0
At least 1 AE resulting in study agent discontinuation	26 (9.7)	3 (1.1)	4 (1.5)	7 (2.9)	8 (3.7)	0	2 (1.0)	2 (1.5)	0
All infections of special interest§	43 (16.0)	14 (5.2)	13 (5.0)	8 (3.3)	6 (2.7)	7 (3.5)	11 (5.7)	6 (4.6)	0
Serious	5 (1.9)	1 (0.4)	1 (0.4)	1 (0.4)	0	1 (0.5)	1 (0.5)	0	0
Opportunistic infections of special interest¶	16 (6.0)	3 (1.1)	3 (1.2)	4 (1.6)	0	3 (1.5)	6 (3.1)	2 (1.5)	0
Serious	0	0	0	0	0	0	0	0	0
All herpes zoster	27 (10.1)	9 (3.4)	6 (2.3)	4 (1.6)	4 (1.8)	5 (2.5)	7 (3.6)	3 (2.3)	0
Opportunistic¶	9 (3.4)	1 (0.4)	2 (0.8)	2 (0.8)	0	2 (1.0)	5 (2.6)	2 (1.5)	0
Serious	1 (0.4)	0	1 (0.4)	0	0	0	0	0	0
Malignant neoplasms (excluding nonmelanoma skin cancer)	10 (3.7)	0	1 (0.4)	4 (1.6)	2 (0.9)	0	0	2 (1.5)	1 (1.5)
Postinfusion systemic reactions#	50 (18.7)	23 (8.6)	11 (4.2)	7 (2.9)	5 (2.3)	4 (2.0)	6 (3.1)	5 (3.8)	1 (1.5)
Any depression/suicide/self-injury§	73 (27.2)	25 (9.3)	22 (8.5)	17 (7.0)	6 (2.7)	8 (4.0)	3 (1.6)	4 (3.1)	1 (1.5)
Deaths	2 (0.7)	0	1 (0.4)	0	1 (0.5)	0	0	0	0

* Values are the number (%) of patients. Patients reporting multiple adverse events (AEs) within a study year are only counted once in each of the appropriate categories.
† Possibly, probably, or definitely related.
‡ Two most frequently occurring AE system organ classes presented.
§ Per custom Medical Dictionary for Regulatory Activities (MedDRA) query.
¶ Per adjudication by GlaxoSmithKline.
# Per custom MedDRA query, broad search.

patients (9.7%), with the majority (n = 22) of these occurring in the first 4 years of the study. With the exception of intraductal proliferative breast lesion (n = 2), all AEs that led to study drug discontinuation were different. The most common AEs (occurring in ≥25% of patients) were arthralgia (108 of 268 [40.3%]), nausea (88 of 268 [32.8%]), headache (86 of 268 [32.1%]), and infections, including bacterial upper respiratory tract infection (77 of 268 [28.7%]), viral upper respiratory tract infection (76 of 268 [28.4%]), and bacterial urinary tract infection (70 of 268 [26.1%]). At least 1 serious AE was reported in 112 of 268 patients (41.8%), and at least 1 severe AE (grade 3 or grade 4 events listed as life-threatening) was reported in 100 of 268 patients (37.3%). Two deaths occurred (0.7%); neither was considered study drug–related (hypertensive heart disease, polydrug toxicity [later adjudicated as suicide]). AEs of special interest are summarized in Table 2. Sixteen patients acquired an opportunistic infection (none categorized as serious), and 3 incidents

of suicidal behavior (1.1%) were reported. Overall, the incidence of AEs, treatment-related AEs, serious AEs, and severe AEs remained stable or declined from study year 1 to study year 7+.

Clinical laboratory evaluations and vital signs. Lymphocyte count was the only hematologic measure in which ≥10% of patients had either grade 3 or grade 4 values during the study; 50 of 177 patients (28.2%) had a grade 3 value. The percentage of patients who had at least a 2-grade shift from baseline in clinical chemistry studies (liver function, electrolytes, and other chemistry studies) was generally stable or declined over time, not exceeding 12% postbaseline. The percentage of patients with grade 3 or grade 4 values at any time postbaseline did not exceed 5% for any clinical chemistry parameter or urinalysis, and no trends of clinical concern were noted. During the study, 7 of 268 patients (2.6%) had a grade 3 value for IgG, and none of these patients experienced a serious or severe infection. Two patients had a persistent positive anti-human antibody response that

occurred during at least 2 consecutive assessments or once at the final assessment, although no patient had >2 consecutive positive results. Mean diastolic and systolic blood pressures were stable over time.

Organ damage. The mean ± SD SDI score was 1.2 ± 1.51 at baseline. At study year 7 the mean ± SD SDI score had increased by 0.4 ± 0.68.

Efficacy. SRI response. An SRI response had been achieved by 96 of 229 patients (41.9%) and 90 of 119 patients (75.6%) overall at the study year 1 and study year 7 midpoints, respectively (Figure 2A). Withdrawals between these 2 time points were examined post hoc, along with the occurrence of new responses, to account for the decrease in absolute number of responders. Of the patients who withdrew (113 of 268;

modified ITT population) between these 2 time points, 34 of 113 (30.1%) were responders at the study year 1 midpoint. Of the 90 patients who were SRI responders at the study year 7 midpoint, 35 of them (38.9%) had not been responders at the study year 1 midpoint (52 patients [57.8%] were responders at the study year 1 midpoint).

SELENA–SLEDAI score. The overall percentage of patients with a ≥4-point reduction from baseline in the SELENA–SLEDAI score increased from 44.4% (104 of 234 patients) to 78.2% (93 of 119 patients) at the study year 1 and study year 7 midpoints, respectively (Figure 2B). The overall mean ± SD percentage reduction from the baseline SELENA–SLEDAI score (7.8 ± 3.86) increased from 27.1 ± 48.29% at the study
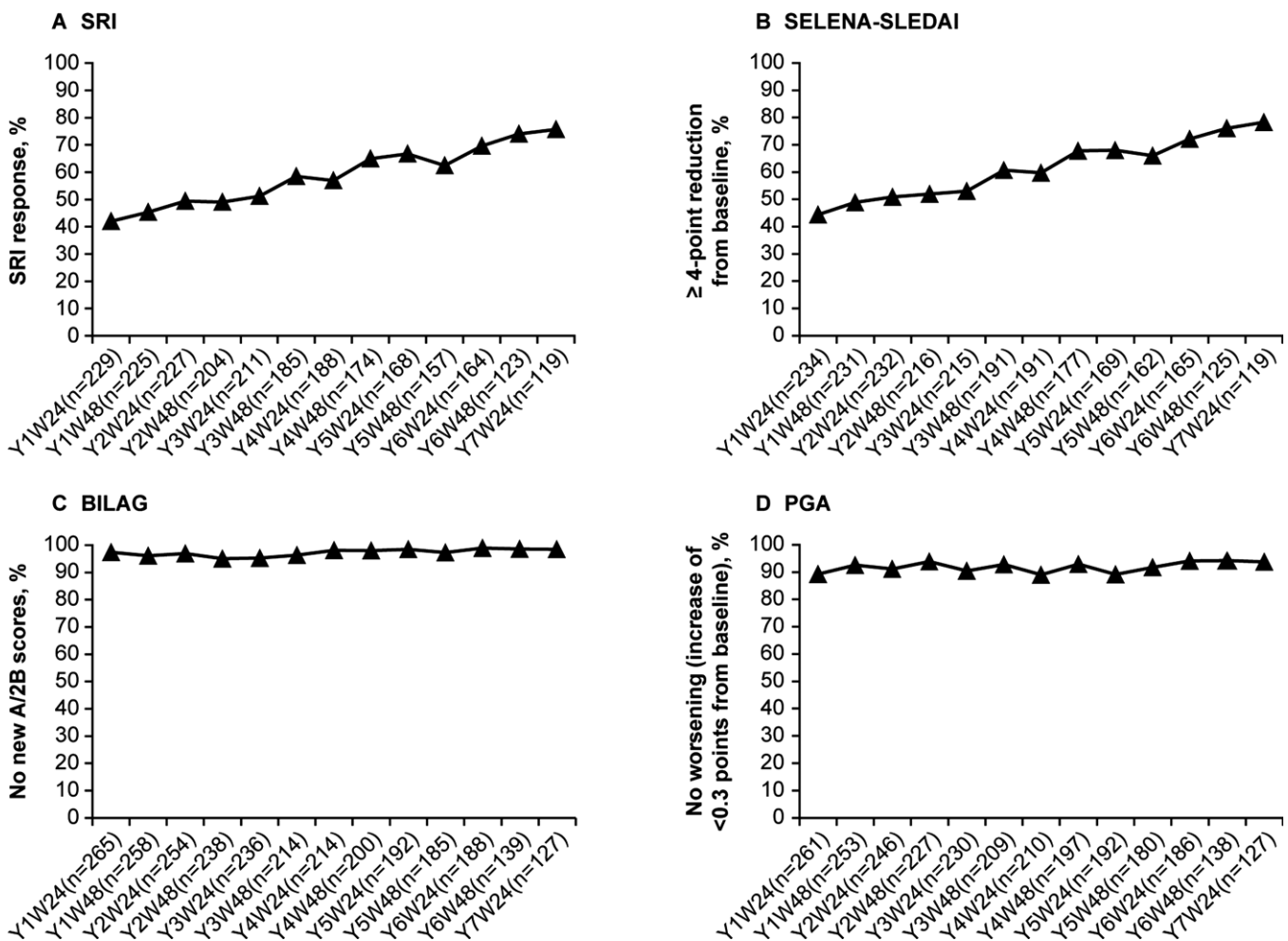

Figure 2. Efficacy end points. **A,** Systemic Lupus Erythematosus Responder Index (SRI) response. **B,** Safety of Estrogens in Lupus Erythematosus National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index (SELENA–SLEDAI) score. **C,** British Isles Lupus Assessment Group (BILAG) score. In **A** and **B**, patients with baseline SELENA–SLEDAI scores of <4 were excluded from the analyses. No new A/2B scores = no new BILAG A organ domain score and no more than 1 new BILAG B organ domain score. **D,** Physician's global assessment of disease activity (PGA) score. Y1W24 = year 1, week 24.

year 1 midpoint (n = 252) to 64.9 ± 37.46% at the study year 7 midpoint (n = 125).

BILAG worsening. At baseline, the percentage of patients with at least 1 BILAG A or 2 BILAG B organ domain scores was 51.1% (137 of 268). Overall, at each visit, ≥95% of patients had no new BILAG A organ domain score and no more than 1 new BILAG B organ domain score. At the study year 1 midpoint, 258 of 265 patients (97.4%) had no new BILAG A organ domain score and no more than 1 new BILAG B organ domain score. This remained stable throughout the study, with 125 of 127 patients (98.4%) meeting this criterion at the study year 7 midpoint (Figure 2C). Among patients with a postbaseline flare assessment, 33 of 267 (12.4%) and 84 of 267 (31.5%) had at least 1 BILAG flare by the study year 1 and study year 7 midpoints, respectively.

Worsening in physician's global assessment of disease activity. The overall percentage of patients with no new worsening (increase of <0.30 points) from baseline in the physician's global assessment of disease activity was ≥89% up to the study year 7 midpoint visit (119 of 127 patients [93.7%]) (Figure 2D).

SFI flare. By the study year 1 midpoint, 149 of 267 patients (55.8%) had experienced at least 1 SFI flare, and 15 of 267 (5.6%) had experienced at least 1 severe flare. Up to and including the study year 7 midpoint visit, these percentages increased to 92.5% (247 of 267) and 20.6% (55 of 267), respectively (cumulative). Of the 55 patients with a severe flare at the study year 7 midpoint, new/worse severe symptoms were experienced by 23.6% of patients (13 of 55), 63.6% of patients (35 of 55) had an increase in daily prednisone dose to >0.5 mg/kg, and 38.2% of patients (21 of 55) had 1 new medication for SLE activity. An increase to a score of ≥2.5 on the physician's global assessment of disease activity was recorded in 5 of 55 patients (9.1%), and 10 of 55 patients (18.2%) were hospitalized for SLE activity.

Prednisone use. Among patients receiving concomitant prednisone (n = 77), the mean decrease from baseline in prednisone dose at the study year 7 midpoint was 31.4% (Figure 3). The percentage of patients with a baseline prednisone dose of >7.5 mg/day whose dose was reduced to ≤7.5 mg/day was 50.0% (32 of 64) at the study year 3 midpoint, 39.5% (15 of 38) at study year 7, and 58.3% (7 of 12) at study year 8. Some patients (23 of 173 [13.3%]) discontinued prednisone permanently during the study (post hoc analyses).

Biomarkers. At baseline, 135 of 268 patients (50.4%) were anti-dsDNA positive (≥30 IU/ml), 86 of 268 (32.1%) had low C3 levels, and 98 of 268 (36.6%) had low C4 levels. Post hoc analyses showed that
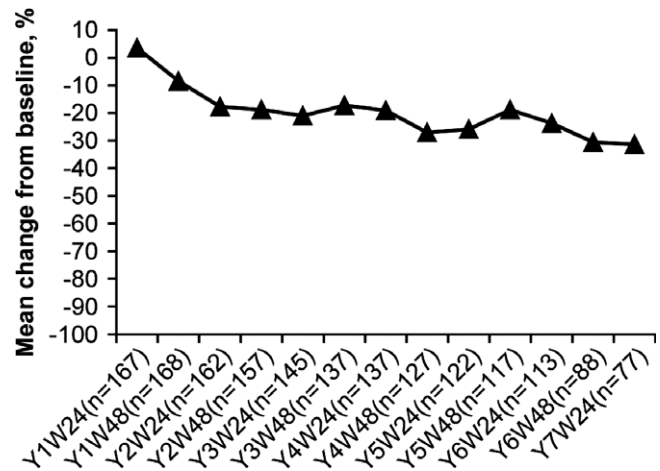

Figure 3. Mean percentage change from baseline in prednisone dose. Y1W24 = year 1, week 24.

among those who were anti-dsDNA positive at baseline, levels in 23 of 135 (17.0%) normalized during the study, while levels in 10 of 86 (11.6%) with low C3 and levels in 20 of 98 (20.4%) with low C4 normalized. Overall, mean levels of anti-dsDNA antibodies decreased by 44.1% (n = 123) from baseline to study year 7 (Table 3), and mean C3 and C4 levels increased by 18.9% (n = 123) and 50.0% (n = 123), respectively.

Among the 36 patients with elevated baseline proteinuria (>0.5 gm/24 hours), mean levels in 14 patients improved by 69.1% from baseline to the study year 7 midpoint. Normal levels were achieved by 11 of 34 of these patients (32.4%) at the study year 1 midpoint and by 9 of 14 of these patients (64.3%) at the study year 7 midpoint.

IgG levels decreased by 29.0% (n = 112) from baseline to study year 7. The median percentage change from baseline in CD20+ B cells was −83.22% (n = 107) at the study year 7 midpoint (Table 3). Reductions were also observed for CD19+, naive, activated, plasma, SLE subset, and plasmacytoid B cells. The median percentage change from baseline in memory B cells was 87.65% (n = 244) at the study year 1 midpoint and −67.18% (n = 106) at the study year 7 midpoint. Although variable over time, the median percentage change from baseline in short-lived plasma B cells was −47.50% (n = 114) at the study year 7 midpoint.

DISCUSSION

Long-term treatment with belimumab was associated with a stable or decreased incidence of AEs and sustained efficacy across 7 study years of exposure, similar to the safety and efficacy profiles of belimumab

Table 3. Biomarkers observed at baseline and change from baseline (modified intent-to-treat population)*

Biomarker	Observed value at baseline	Study year 1 midpoint (observed)	Study year 1 midpoint (% change from baseline)	Study year 7 midpoint (observed)	Study year 7 midpoint (% change from baseline)
Anti-dsDNA, IU/ml	88.10 ± 73.565/268	78.53 ± 67.774/253	−7.61 ± 19.068/253	78.50 ± 292.110/123	−44.07 ± 148.281/123
Complement level, gm/liter					
C3	1.068 ± 0.310/268	1.103 ± 0.296/253	6.74 ± 26.443/253	1.226 ± 0.311/123	18.90 ± 30.975/123
C4	0.198 ± 0.099/268	0.220 ± 0.101/253	19.82 ± 38.678/253	0.250 ± 0.101/123	49.96 ± 96.800/123
Proteinuria level, gm/24 hours					
All patients	0.31 ± 0.561/268	0.28 ± 0.666/251	10.44 ± 84.097/251	0.15 ± 0.170/120	−11.26 ± 75.237/120
Patients with >0.5 gm/24 hours at baseline	1.36 ± 1.013/36	1.17 ± 1.534/34	−17.51 ± 81.675/34	0.41 ± 0.368/14	−69.09 ± 25.846/14
IgG, gm/liter	15.16 ± 6.062/268	12.93 ± 4.704/252	−12.80 ± 14.078/252	10.09 ± 3.745/112†	−28.97 ± 16.733/112†
B cells/μl					
CD19+	114.00 (58.00, 191.00)/265	69.00 (36.00, 113.00)/253	−32.56 (−57.58, 5.88)/250	18.50 (8.00, 34.00)/122	−82.73 (−89.01, −68.73)/120
CD20+	112.50 (55.00, 189.00)/262	68.00 (35.00, 113.0)/251	−31.82 (−56.40, 9.15)/245	20.00 (10.00, 36.00)/111	−83.22 (−89.24, −69.05)/107
Naive (CD20+CD27−)	88.00 (38.00, 155.00)/262	36.00 (16.00, 64.00)/251	−55.56 (−73.74, −29.41)/245	13.00 (6.00, 24.00)/111	−87.39 (−92.77, −73.53)/107
Activated (CD20+CD69+)	190.00 (106.00, 320.00)/257	131.00 (72.00, 206.00)/247	−33.35 (−65.19, 36.11)/240	3.00 (1.00, 5.00)/122	−98.85 (−99.62, −96.45)/116
Memory (CD20+CD27+)	17.00 (8.00, 28.00)/262	30.00 (14.00, 55.00)/251	87.65 (27.43, 167.54)/244	6.00 (3.00, 12.00)/111	−67.18 (−80.00, −47.06)/106
Plasma (CD20−CD138+)	41.00 (17.00, 128.00)/261	31.00 (12.00, 69.00)/251	−37.20 (−66.75, 27.50)/244	4.50 (1.00, 11.00)/122	−92.31 (−98.05, −73.68)/118
SLE subset (CD19+CD27^bright CD38^bright)	17.00 (6.00, 45.00)/262	13.00 (6.00, 34.00)/251	−16.13 (−71.43, 88.89)/243	9.00 (3.00, 25.00)/122	−50.00 (−81.44, 28.57)/117
Short-lived plasma (CD19+CD20−CD27^high/+)	16.00 (7.00, 46.00)/258	13.00 (5.00, 32.00)/247	−32.29 (−73.13, 61.54)/238	9.00 (4.00, 24.00)/122	−47.50 (−79.17, 41.67)/114
Plasmacytoid (CD20+CD138+)	95.00 (58.00, 182.00)/261	64.00 (31.00, 108.00)/251	−32.49 (−73.33, 32.00)/243	2.00 (1.00, 5.00)/122	−98.00 (−99.61, −94.22)/117

* Values are the mean ± SD/number of patients or median (interquartile range)/number of patients. Anti-dsDNA = anti–double-stranded DNA; SLE = systemic lupus erythematosus.
† Study year 7 end.

previously established during studies of patients with SLE (12–14,22). In the present study, three-fourths of patients were SRI responders at the study year 7 midpoint, an observation that is consistent with the phase II continuation study, in which 65% of patients had achieved an SRI response by study year 7 (73% in the completer analysis) (12).

Secondary analyses of the BLISS studies have shown that patients treated with belimumab (plus standard therapy) experienced reduced rates of severe flares when compared with those receiving placebo (plus standard therapy) (13,14). In the BLISS-52 and BLISS-76 studies, rates of severe SFI flare were 14% (40 of 290 patients) and 21% (56 of 273 patients), respectively (13,14), among patients who received 10 mg/kg belimumab. In this continuation study, the percentage of patients experiencing a new severe SFI flare between the study year 1 and study year 7 midpoints was low; the cumulative count increased from 15 of 267 patients (5.6%) to 55 of 267 patients (20.6%) during this period. In the phase II continuation study, the percentages of severe flares were also low, decreasing from 7% to 2% across each year of belimumab treatment (12).

Organ damage accrual in this continuation study was low when compared with prospective SLE inception cohorts measuring damage accrual (23–25), with a mean increase in SDI of 0.4 over 7 study years. However, while observational cohorts included the full spectrum of patients, the BLISS studies excluded patients with severe lupus nephritis and central nervous system disease (13,14), manifestations that may result in higher rates of damage accrual (26,27). These exclusions, in addition to treatment with belimumab, could account, in part, for the reported lower rates of organ damage.

One of the major goals of SLE therapy is to reduce corticosteroid exposure (28). In the current study, mean prednisone dose decreased over time, and approximately one-eighth of patients were able to discontinue prednisone.

Quantitative analysis of B cell phenotypes performed in this study represents the first evaluation of long-term changes in B cells in response to belimumab treatment. The results presented are consistent with those of a small 2-year study that investigated the effects of belimumab treatment on levels of B cell subsets (29). Over the duration of the study, there was a decrease in levels for the majority of B cell subsets, but no subsets were completely depleted. As demonstrated in that earlier study (29), memory B cells were initially found to increase in response to belimumab, while a decrease was seen after study year 1.

There are several limitations to the interpretation of these data, primarily the open-label design with no placebo control group. In addition, selection bias could have been responsible for enriching the study population with patients more likely to respond well to treatment over time. Furthermore, approximately one-third of the study population was treated with placebo during the parent study. Since these patients continued to receive placebo (and standard therapy) for 76 weeks before entering this extension study, they may have entered this extension study with more benign disease (32% of patients in the placebo arm withdrew from the parent study). However, the post hoc analysis did not indicate an imbalance in SLE disease activity or characteristics at baseline between those who withdrew over the course of the study and those who completed. In addition, the decline in the number of patients starting each yearly interval was similar between patients initially treated with belimumab in the parent study and those treated with placebo. Withdrawals from the study were more prevalent among nonresponders, although the reasons for withdrawal among nonresponders cannot be confirmed. The impact of the withdrawals may have created responder bias by affecting the composition of the remaining study population.

Although the duration of treatment with belimumab 10 mg/kg differed (depending on initial treatment assignment), all treatment groups were pooled for analysis. In addition, low numbers of patients for some analyses, particularly at later time points, may confound interpretation. Data on AEs of special interest, particularly rates of infection, should be interpreted with caution, as fewer patients contributed to the denominator in later intervals.

This study demonstrates the long-term benefits of belimumab in addition to standard therapy in patients with active SLE. Belimumab was well tolerated, and patients benefited from an overall decrease in disease activity. Moreover, prednisone use declined, and accrual of organ damage was low.

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, Fettiplace, Roth, Gordon.

Acquisition of data. Furie, Wallace, Aranow.
Analysis and interpretation of data. Furie, Wallace, Aranow, Fettiplace, Wilson, Mistry, Roth, Gordon.

ROLE OF THE STUDY SPONSOR

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