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Safety and Efficacy of Belimumab Plus Standard Therapy for Up to Thirteen Years in Patients With Systemic Lupus Erythematosus

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Objective. To investigate the long-term safety and efficacy of intravenous (IV) belimumab plus standard of care (SOC) therapy for systemic lupus erythematosus (SLE) in patients with active, autoantibody-positive SLE.

Methods. The study was designed as a multicenter, open-label, continuation study of IV belimumab given every 4 weeks in conjunction with SOC therapy in patients with SLE who completed a phase II, double-blind study. Adverse events (AEs) and laboratory data were monitored from the first belimumab dose (in either study) until 24 weeks after the final dose. Efficacy assessments included SLE Responder Index (SRI) and flare index scores (each assessed at 16-week intervals) and glucocorticoid use (assessed at 4-week intervals).

Results. Of the 476 patients in the parent study, 298 (62.6%) entered the continuation study, of whom 96 (32.2%) remained in the study. Patients received belimumab for up to 13 years (median duration of exposure 3,334.0 days [range 260–4,332 days], total belimumab exposure 2,294 patient-years, median number of infusions 115.5 [range 7–155]). The percentage of patients with AEs each year remained stable or decreased. Normal serum IgG levels were maintained in the majority of patients over the study, and the rate of infections remained stable. The percentage of patients who achieved an SRI response increased from 32.8% (year 1) to 75.6% of those remaining on treatment at year 12. The glucocorticoid dose was decreased in patients who had been receiving >7.5 mg/day at baseline.

Conclusion. This study is the longest to date to assess belimumab treatment in patients with SLE in clinical trials. Belimumab was well tolerated with no new safety concerns, and efficacy was maintained in patients who continued the study. For patients who initially exhibited a satisfactory response to belimumab, the treatment continues to be well tolerated and provides long-term disease control.

INTRODUCTION

Intravenous (IV) belimumab (10 mg/kg) is approved for the treatment of active, autoantibody-positive systemic lupus erythematosus (SLE) in more than 60 countries, including the US, Japan, and countries in Europe (1–3). A phase II, placebo-controlled, dose-ranging trial (GlaxoSmithKline trial no. LBSL02; ClinicalTrials.gov identifier NCT00071487) of IV belimumab administered in conjunction with standard of care (SOC) therapy in 449 patients with active, autoantibody-positive SLE demonstrated that belimumab was well tolerated through 52 weeks (4). This study also informed the design of phase III trials (5,6) and the development of the SLE Responder Index (SRI) (7). Two pivotal phase III trials further demonstrated the efficacy and safety of IV belimumab plus SOC therapy for up to 76 weeks (5,6).

To investigate the long-term safety and efficacy of belimumab plus SOC therapy, a continuation study of LBSL02 was conducted. Previous interim analyses from this study have shown that belimumab was well tolerated, and disease control was maintained through 7 years (8,9). Herein we report the final analysis of this study, which is currently the longest SLE therapy study measuring the efficacy and safety of IV belimumab (9), in which patients received treatment with belimumab for up to 13 years.

PATIENTS AND METHODS

Study design. The study was designed as a multicenter, open-label, continuation study (GlaxoSmithKline study no. BEL112626; ClinicalTrials.gov identifier NCT00583362) of IV belimumab administered in conjunction with SOC therapy in patients with SLE who had achieved a satisfactory response to belimumab in a phase II, double-blind study (for the study design, see Supplementary Figure 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40861/abstract) (4). Patients who completed the double-blind phase could continue in the open-label, 24-week extension study. In the extension, patients who had received placebo switched to 10 mg/kg IV belimumab, and those previously receiving belimumab either continued at the same dose (1, 4, or 10 mg/kg) or switched to 10 mg/kg, based on their response at the end of the double-blind phase.

Patients who completed the extension study, who had an improvement in score on the physician's global assessment (PhGA) of disease activity compared with baseline (prior to the first dose of belimumab), and who did not develop a severe flare (according to the Safety of Estrogens in Lupus Erythematosus National Assessment [SELENA] version of the SLE Disease Activity Index [SLEDAI] Flare Index [SFI] [10]) in the last 30 days of the extension study were eligible to enter the continuation study. The protocol for the continuation study has been reported previously (8,9). Briefly, all patients received 10 mg/kg IV belimumab every 4 weeks until they withdrew from the study or the criteria for ending the study were met (whichever came first, 10 years from the enrollment of the last patient or ≤100 patients participating in the study). To prevent unnecessary long-term exposure to belimumab for patients who did not benefit from treatment, stopping rules were applied (a complete list of the stopping rules is shown in Supplementary Table 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40861/abstract). Following withdrawal from the study, patients were monitored for an additional 24 weeks.

Institutional review board or ethics committee approval was obtained for all study sites. All patients gave their informed consent before entering the long-term continuation study (8,9).

Assessments. Safety was monitored from the first dose of study treatment until 24 weeks after the final dose, with adverse events (AEs) and laboratory data recorded. Clinical laboratory tests included hematology, chemistry, routine urinalysis, measurement of serum immunoglobulins (IgG, IgA, IgE, and IgM), and antidrug antibody testing. These tests were performed every 8 weeks.

Efficacy assessments were conducted periodically and included the following: percentage of patients with an SRI response (i.e., achievement of the SRI-4 criteria) (7) (at 16-week intervals), disease activity scores on the SELENA-SLEDAI (10) and the British Isles Lupus Assessment Group (BILAG) Index (11) (at 16-week intervals), the PhGA (at 8-week intervals), SFI scores of disease flare and severe disease flare (at 16-week intervals), change in glucocorticoid use (at 4-week intervals), and serologic measurements (including serum levels of complements C3 and C4 and autoantibodies) (at 16-week intervals). Glucocorticoid doses are reported in prednisone equivalent units. Low disease activity was defined as a SELENA-SLEDAI score of ≤2 and a prednisone dose of ≤5 mg/day.

Statistical analysis. All data analyses were conducted in the modified intent-to-treat population, defined as all patients who received at least 1 dose of belimumab in the continuation study. No formal statistical hypothesis testing was performed, and all analyses were exploratory. All analyses were performed using descriptive statistics. Post hoc analyses included AE rates (per 100 patient-years) by preferred term, last observation carried forward (LOCF) for SRI response rates among patients who withdrew from the study, categorical analyses of SELENA-SLEDAI and PhGA disease activity scores, the cumulative time that the patients' prednisone dose was ≤7.5 mg/day, the number of patients with low disease activity at each study visit, and determination of normalization of anti–double-stranded DNA (anti-dsDNA) antibody and C3/C4 complement levels.

Baseline data were recorded prior to the first dose of belimumab (in either the parent study or extension study for those who previously received placebo). Data analyses were performed using SAS software, version 9.4 (SAS Institute).

RESULTS

Study population and disposition of the patients.
Patients with SLE (n = 476) were randomized in the parent study to receive IV belimumab or placebo, which was added to SOC therapy. Of these, 298 patients (62.6%) entered the continuation study, of whom 96 (32.2%) remained in the study to the end (year 13) (Figure 1A) and 88 (29.7%) remained in the study for ≥11 years. Total belimumab exposure was 2,294 patient-years.

The median duration of exposure was 3,334.0 days (range 260–4,332 days), and the median number of infusions was 115.5 (range 7–155). Patient self-withdrawal was the most common form of withdrawal (Figures 1A and B); the most frequent reasons for this were a desire to become pregnant, and difficulties attending the clinic due to location, travel, or time constraints. Withdrawal due to lack of efficacy seldom occurred throughout the study, with the frequency of withdrawal because of ineffi-
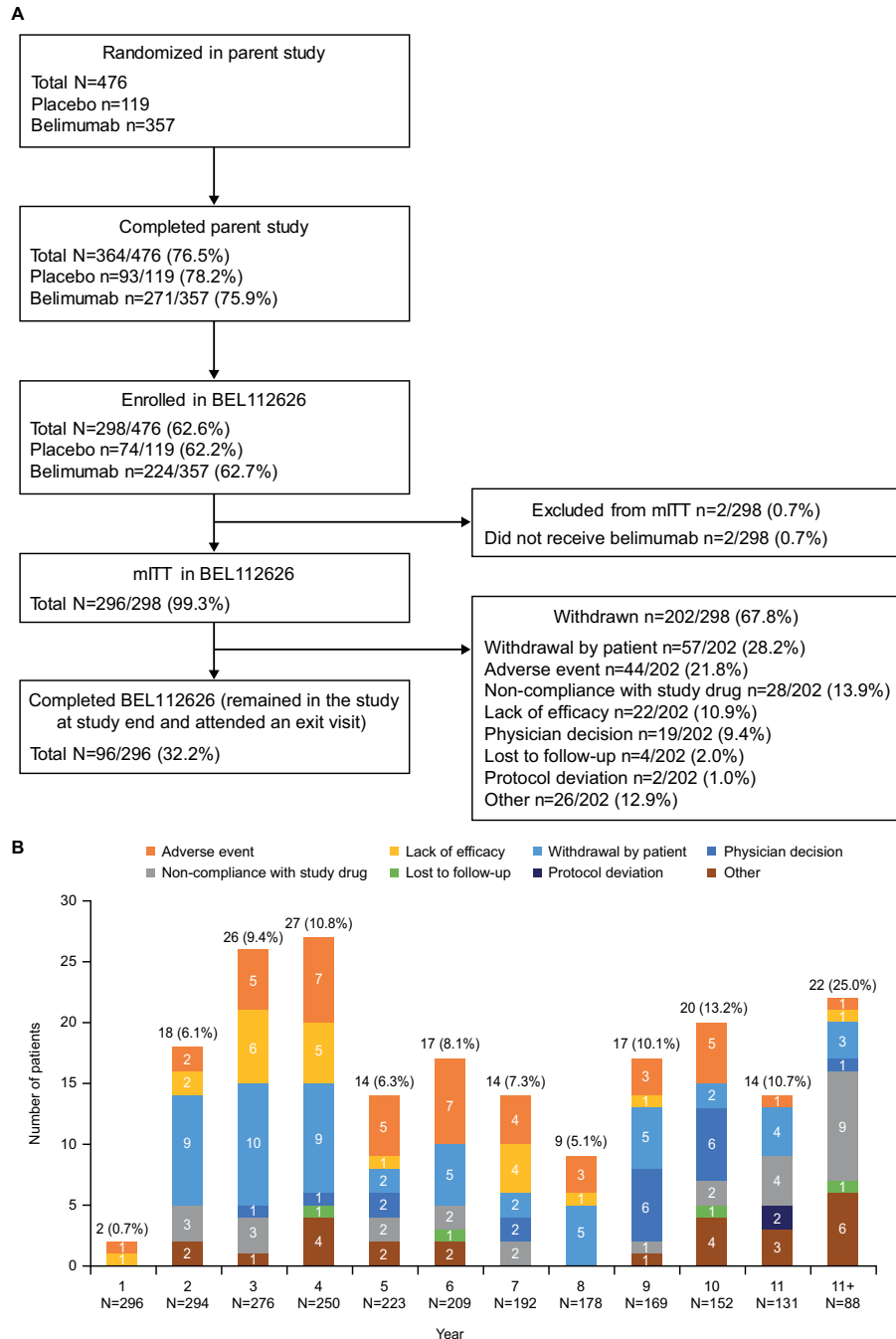
Figure 1. **A**, Disposition of the patients with systemic lupus erythematosus randomized to receive placebo or belimumab. **B**, Frequency and reasons for withdrawals per study year. Values are the total number (%) of patients who withdrew, based on the number of patients starting each study year. mITT = modified intent-to-treat.

cacy reaching a maximum of 6 patients in year 3. At years 5, 7, and 10, the percentages of patients remaining in the study were 70.1%, 60.1%, and 44.3%, respectively.

Baseline demographics and disease characteristics of the patients have been reported previously (8,9). The majority of patients were female (93.2%), and the mean ± SD age was 43.0 ± 11.58 years (Table 1). At baseline, the mean ± SD duration of SLE was 9.1 ± 7.8 years, the mean ± SD SELENA-SLEDAI score was 8.4 ± 4.68. With regard to adjunct therapies, 31.1% of patients were receiving >7.5 mg/day prednisone, and 35.5% were not receiving glucocorticoids. Among the study patients, 81.3% were antinuclear antibody positive.

Safety. *Adverse events.* The percentage of patients reporting AEs each year remained stable or decreased throughout the study (Table 2; see also Supplementary Table 2 at http://onlinelibrary.wiley.com/doi/10.1002/art.40861/abstract). The most frequent AEs (≥15.0 per 100 patient-years) were arthralgia (29.3 per 100 patient-years), upper respiratory tract infection (29.0 per 100 patient-years), sinusitis (16.9 per 100 patient-years), urinary tract infection (16.2 per 100 patient-years), and headache (15.0 per 100 patient-years). The rates of the most frequent AEs were stable or declined overall from years 1 to 11 and onward to the study end (see results in Supplementary Table 3 at http://onlinelibrary.wiley.com/doi/10.1002/art.40861/abstract). The most common serious AEs (≥0.5 events per 100 patient-years) were pneumonia (0.9 per 100 patient-years), osteoarthritis (deemed a serious AE because of the need for hospitalization for elective surgical management; 0.8 per 100 patient-years), noncardiac chest pain (0.7 per 100 patient-years), pyrexia (0.6 per 100 patient-years), cellulitis, chronic obstructive pulmonary disease, abdominal pain, viral gastroenteritis, and vomiting (each 0.5 per 100 patient-years).

Forty-four patients (14.9%) discontinued treatment with belimumab or withdrew from the study because of an AE. The AEs that resulted in discontinuation or withdrawal of more than 1 patient were invasive ductal breast carcinoma (3 patients [1.0%]) and hypogammaglobulinemia (2 patients [0.7%]).

The rate of serious infections and infestations remained steady from year 1 (3.7 per 100 patient-years) through year 11 (6.7 per 100 patient-years) (Table 2). The rate of infections of special interest was also stable throughout the study (5.1 per 100 patient-years) (Table 2). The rate of malignant neoplasms, excluding nonmelanoma skin cancer, was 0.6 per 100 patient-years; no events were reported in years 1, 2, 8, and 11 and beyond year 11; the rate of malignant neoplasms was highest in year 10 (2.1 per 100 patient-years). There were no cases of progressive multifocal leukoencephalopathy (PML) in this study.

The rate of depression was 9.8 per 100 patient-years (237 events). Six events of suicide/self-injury occurred (0.2 per 100 patient-years), 4 of which were serious, with 1 resulting in death. There were 7 deaths in the study, and 1 during the follow-up period. Causes of death were pneumonia (2 patients [1 due to an opportunistic infection]), cardiac arrest, coronary artery

Table 1. Baseline (prior to the first dose of belimumab) demographic and clinical characteristics of the 296 patients in the study population*

Female, no. (%)	276 (93.2)
Age, mean ± SD years	43.0 ± 11.58
Ethnicity, no. (%)	
Hispanic or Latino	54 (18.2)
Not Hispanic or Latino	242 (81.8)
Race, no. (%)	
White	215 (72.6)
Black or African American	68 (23.0)
Other	13 (4.4)
Disease duration, mean ± SD years	9.1 ± 7.80
SELENA-SLEDAI	
Mean ± SD score	8.4 ± 4.68
Score ≤9, no. (%)	190 (64.2)
Score ≥10, no. (%)	106 (35.8)
BILAG score at least 1A or 2B, no. (%)	168 (56.8)
PhGA score, mean ± SD	1.30 ± 0.571
SFI flare, no. (%)†	
Flare score of at least 1	47 (15.9)
Severe flare score of at least 1	9 (3.0)
Glucocorticoids, no. (%)	
None	105 (35.5)
≤7.5 mg/day prednisone equivalent dose	99 (33.4)
>7.5 mg/day prednisone equivalent dose	92 (31.1)
Low C3 and/or low C4 serum levels, no. (%)‡	135 (46.1)
Anti-dsDNA antibody positive, no. (%)§	149 (50.3)
ANA titer, no. (%)¶	
≥80	208 (81.3)
<80	48 (18.8)

* BILAG = British Isles Lupus Assessment Group (index of disease activity); PhGA = physician's global assessment (of disease activity).
† For the Safety of Estrogens in Lupus Erythematosus National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) Flare Index (SFI), patients who received belimumab in the double-blind phase, any time prior to study entry, and patients who received placebo in the double-blind phase, between the last visit in the double-blind phase and first dose of belimumab in the open-label phase, were assessed.
‡ Low C3 was defined as <90 mg/dl. Low C4 was defined as <16 mg/dl. Data were available for 293 patients.
§ Positivity for anti–double-stranded DNA (anti-dsDNA) antibodies was defined as serum levels of ≥30 IU/ml.
¶ Data for antinuclear antibody (ANA) titers were available for 256 patients.

disease, acute respiratory distress syndrome, respiratory failure, retroperitoneal hemorrhage, and suicide.

Clinical and laboratory parameters. Of the hematology parameters investigated (activated partial thromboplastin time, hemoglobin, neutrophil count, platelet count, and prothrombin time), the only parameter for which ≥10% of patients had a

Table 2. Incidence of AEs overall and by study year*

| Event	Overall (2,416 pt-yrs)					Study year							
		1 (295 pt-yrs)	2 (289 pt-yrs)	3 (260 pt-yrs)	4 (236 pt-yrs)	5 (218 pt-yrs)	6 (199 pt-yrs)	7 (185 pt-yrs)	8 (171 pt-yrs)	9 (160 pt-yrs)	10 (152 pt-yrs)	11 (104 pt-yrs)	11+ (36 pt-yrs)†
AEs	18,259 (755.8)	3,554 (1,203.1)	2,796 (967.9)	2,083 (801.7)	1,639 (694.6)	1,424 (653.3)	1,319 (661.6)	1,357 (733.3)	1,228 (717.4)	1,047 (656.0)	861 (612.8)	629 (603.4)	154 (426.7)
AEs resulting in treatment discontinuation	44 (1.8)	2 (0.7)	3 (1.0)	3 (1.2)	7 (3.0)	5 (2.3)	6 (3.0)	6 (3.2)	1 (0.6)	3 (1.9)	5 (3.6)	2 (1.9)	0
At least 1 serious AE	719 (29.8)	55 (18.6)	65 (22.5)	91 (35.0)	47 (19.9)	93 (42.7)	65 (32.6)	66 (35.7)	63 (36.8)	46 (28.8)	47 (33.5)	27 (25.9)	19 (52.6)
Serious infections/ infestations	134 (5.5)	11 (3.7)	15 (5.2)	13 (5.0)	10 (4.2)	9 (4.1)	8 (4.0)	16 (8.6)	12 (7.0)	8 (5.0)	6 (4.3)	7 (6.7)	5 (13.9)
Infections of special interest‡	124 (5.1)	13 (4.4)	19 (6.6)	9 (3.5)	13 (5.5)	12 (5.5)	12 (6.0)	10 (5.4)	10 (5.8)	4 (2.5)	9 (6.4)	5 (4.8)	3 (8.3)
All malignant neoplasms (except nonmelanoma skin cancer)	14 (0.6)	0	0	1 (0.4)	1 (0.4)	4 (1.8)	1 (0.5)	1 (0.5)	0	2 (1.3)	3 (2.1)	0	0
Depression	237 (9.8)	51 (17.3)	36 (12.5)	17 (6.5)	32 (13.6)	18 (8.3)	11 (5.5)	23 (12.4)	19 (11.1)	11 (6.9)	9 (6.4)	3 (2.9)	0
Suicide/self-injury	6 (0.2)	1 (0.3)	1 (0.3)	1 (0.4)	0	2 (0.9)	1 (0.5)	0	0	0	0	0	0
Death§	8 (0.3)	1 (0.3)	0	1 (0.4)	1 (0.4)	0	1 (0.5)	2 (1.1)	0	0	1 (0.7)	0	0

* Values are the number of adverse events (AEs) (rate per 100 patient-years [pt-yrs]).
† Includes AEs that occurred from year 11 to the end of the study (year 13) and the follow-up period.
‡ Includes opportunistic infections, tuberculosis, herpes zoster (recurrent and disseminated), and sepsis.
§ Causes of death: year 1, coronary artery disease; year 3, suicide; year 4, pneumonia; year 6, cardiac arrest; year 7, acute respiratory distress syndrome, respiratory failure; year 10, retroperitoneal hemorrhage. One death (pneumonia) occurred during the follow-up phase.
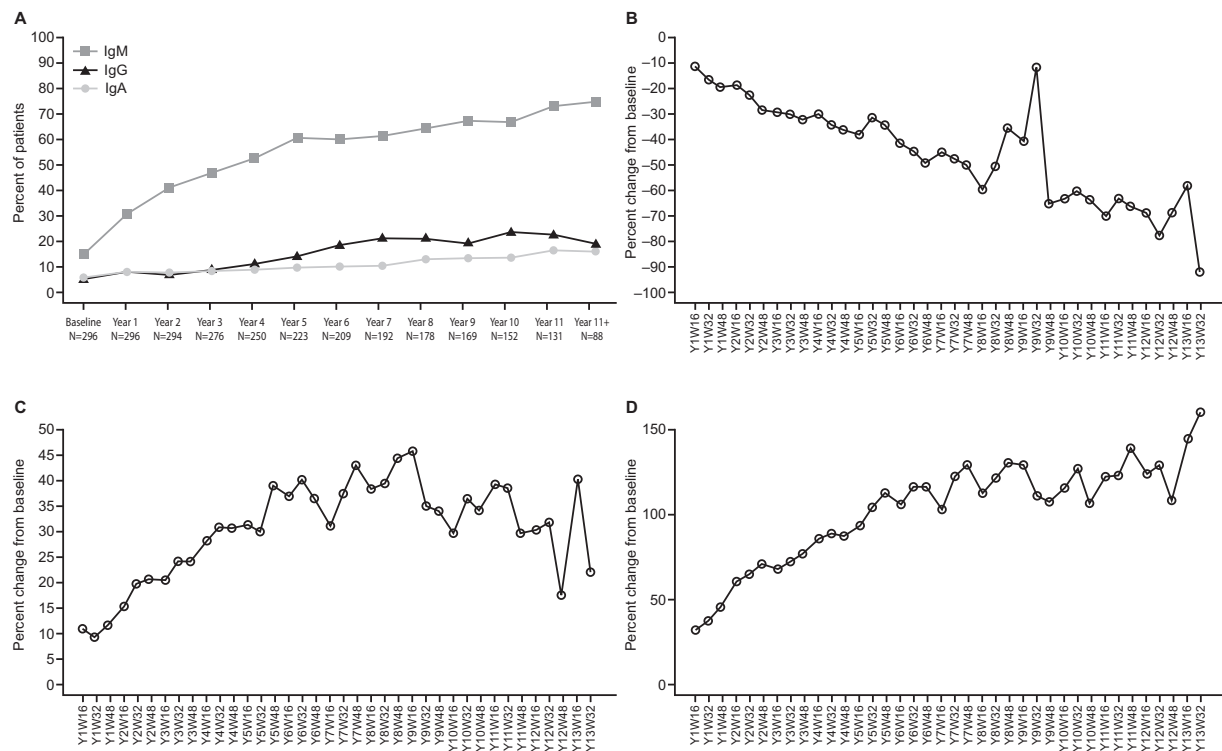
Figure 2. Changes in biomarkers. **A**, Percentage of patients with serum immunoglobulin levels below the lower limit of normal, by study year. For patients with >1 value reported within a year, the last response within the year is summarized. **B**, Percentage change from baseline in anti–double-stranded DNA autoantibody levels among patients who were positive at baseline. **C**, Percentage change from baseline in serum C3 levels among patients who had low C3 (<90 mg/dl) at baseline. **D**, Percentage change from baseline in serum C4 levels among patients who had low C4 (<16 mg/dl) at baseline. W = week; Y = year.

grade 3 (severe) or grade 4 (potentially life-threatening) value was a low neutrophil count (grade 3 in 15.2% of patients [45 of 296] and grade 4 in 2.7% of patients [8 of 296]). Gamma-glutamyl transferase was the only chemistry measurement in which >5% of patients experienced a grade 3 or grade 4 value (grade 3 in 5.7% of patients [17 of 296] and grade 4 in 3.0% of patients [9 of 296]) (complete results for these parameters are shown in Supplementary Table 4, available at http://onlinelibrary.wiley.com/doi/10.1002/art.40861/abstract). With the exception of the protein excretion rate (18 [6.1%] of 296 patients with grade 3 or 4), fewer than 5% of patients had grade 3 or grade 4 abnormalities in any of the urinalysis components (data not shown).

The percentage of patients with serum levels of IgM, IgG, and IgA below the lower limit of normal (LLN) increased during the study (Figure 2A). There were 57.4% (170 of 296 patients), 16.2% (48 of 296 patients), and 13.5% (40 of 296 patients) who had IgM, IgG, and IgA levels below the LLN, respectively, at more than one visit. No serum IgE levels were below the LLN. The majority of patients (65.9% [195 of 296]) had normal serum IgG levels throughout the study; 4.1% (12 patients) had grade 3 IgG values (250–399 mg/dl), and 2.4% (7 patients) had grade 4 IgG values (<250 mg/dl) (see Supplementary Table 4). Of the 19 patients who had grade 3 or grade 4 serum IgG values, 17 (5.7%) had at least a 2-grade shift from baseline.

Although there was a reduction in serum IgG levels during the study, the rate of infections (serious and nonserious) remained stable over time (Table 2). A post hoc analysis showed that 4 of 19 patients with grade 3 or grade 4 IgG abnormalities had a severe and/or serious infection (viral gastroenteritis, urinary tract infection and sepsis, bronchitis, cellulitis) ≤28 days before experiencing the grade 3 or grade 4 reduction in serum IgG levels.

Efficacy. As the number of participants declined, the percentage of patients who achieved an SRI response increased from 32.8% (88 of 268) at year 1, week 16 to 75.6% (68 of 90) at year 12, week 32 (Figure 3A). Among patients who withdrew from the study and had a SELENA-SLEDAI score of ≥4 at baseline, 59.8% (110 of 184) were SRI responders (LOCF) at the time of withdrawal. The percentage of patients with a ≥4-point reduction from baseline in the SELENA-SLEDAI score also increased, from 33.7% (99 of 294) at year 1, week 16 to 76.7% (69 of 90) at year 12, week 32. The percentage of patients achieving a SELENA-SLEDAI score of ≤2 increased throughout the study, from 8.4% (25 of 296) at baseline to 62.2% (46 of 74) at year 12, week 48 (Figure 3B).

The percentage of patients with no new BILAG A organ domain score and no more than 1 new BILAG B organ domain score compared with baseline increased over time, ranging from
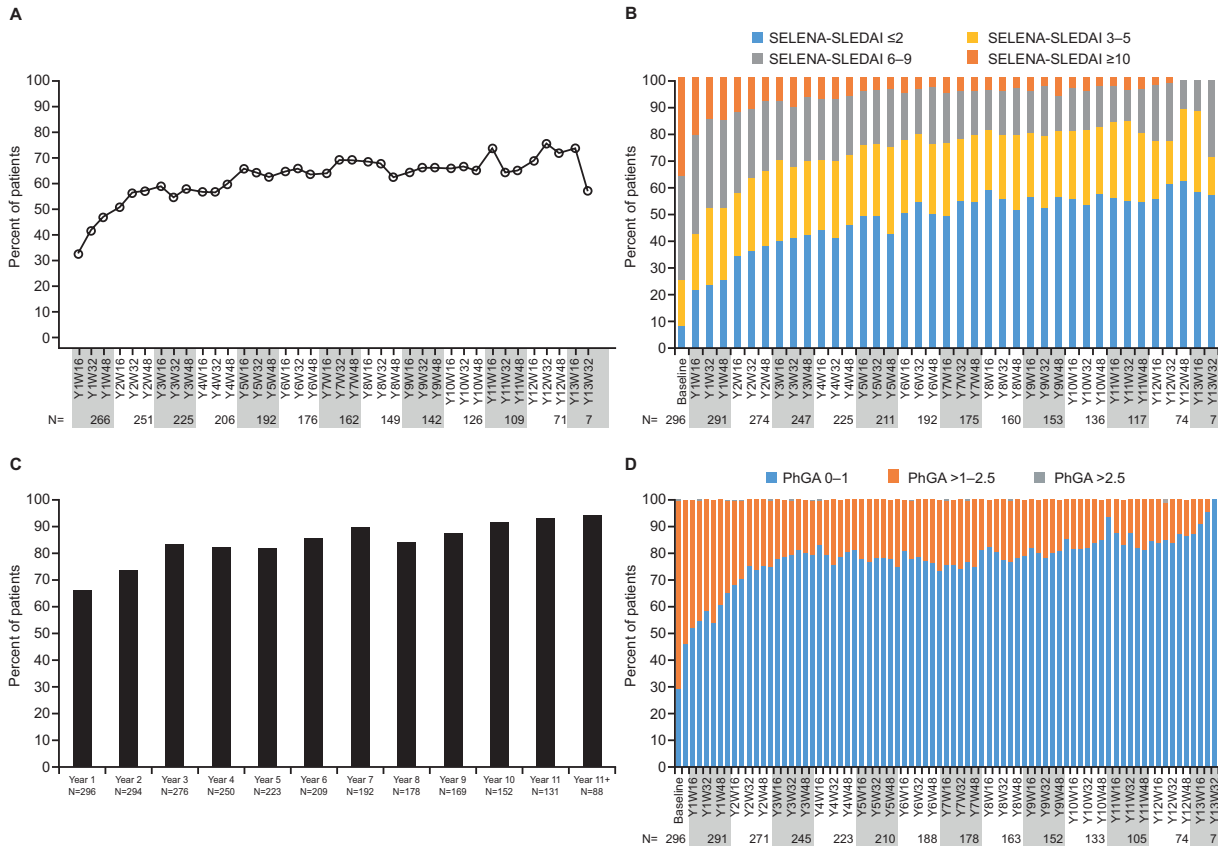
Figure 3. Treatment response measures and percentage of assessed patients with treatment response, according to achievement of the Systemic Lupus Erythematosus (SLE) Responder Index criteria (**A**), 4 categories of disease activity scores on the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) version of the SLE Disease Activity Index (SLEDAI) (**B**), no new British Isles Lupus Assessment Group (BILAG) A organ domain score and no more than 1 new BILAG B organ domain score from baseline (**C**), and 3 categories of scores on the physician's global assessment (PhGA) of disease activity (**D**). Numbers of patients in **A**, **B**, and **D** are from the final time point of each year. W = week; Y = year.

65.9% (195 of 296) during year 1 to 94.3% (83 of 88) at study end (Figure 3C). The percentage of patients with low PhGA disease activity scores (scores of 0 or 1) increased during the study; at all time points, only a few patients had PhGA disease activity scores higher than 2.5 (Figure 3D).

Rates of SFI flares and severe SFI flares were 1.1 per patient-year and 0.1 per patient-year, respectively. The occurrence of flares was highest in year 1 and was consistently low throughout the study (Figure 4A).

At baseline, 190 patients (64.5%) were receiving glucocorticoids; of these, 25 (13.2%) discontinued glucocorticoids for the remainder of the study. The median percentage change from baseline in daily prednisone dose was greatest at year 13, week 24 (88% [range –100 to 33.33%]; n = 16) (Figure 4B). Of the patients receiving >7.5 mg/day prednisone at baseline, the percentage achieving a dose of ≤7.5 mg/day increased over time (Figure 4C) to a maximum of 53.8% (14 of 26 patients) at year 12, week 48. Of the 99 of 296 patients receiving ≤7.5 mg/day prednisone at baseline, 23 (23.2%) maintained a dose of ≤7.5 mg/day throughout the study. The percentage of patients who had an

increase in prednisone dose to >7.5 mg/day increased from year 1, week 8 (3.0% [6 of 200 patients]) to a maximum of 20.4% (11 of 54 patients) at year 12, week 40 (Figure 4C; see also Supplementary Figure 2 at http://onlinelibrary.wiley.com/doi/10.1002/art.40861/abstract).

The percentage of patients achieving low disease activity (a SELENA-SLEDAI score of ≤2 and prednisone dose ≤5 mg/day) increased throughout the study, from 13.9% (41 of 294 patients) at year 1, week 16 to a maximum of 57.1% (4 of 7 patients) at year 13, week 32 (Figure 4D).

Disease activity following withdrawal from the study. Following withdrawal from the study, there was little change in disease activity at follow-up weeks 8 and 24 (see results in Supplementary Table 5, available at http://onlinelibrary.wiley.com/doi/10.1002/art.40861/abstract). The percentage of patients who achieved an SRI response increased slightly from follow-up week 8 (61.9% [122 of 197 patients]) to follow-up week 24 (64.0% [114 of 178 patients]). However, the percentage of patients who developed an SFI flare (week 8, 20.5% [45 of 219 patients]; week
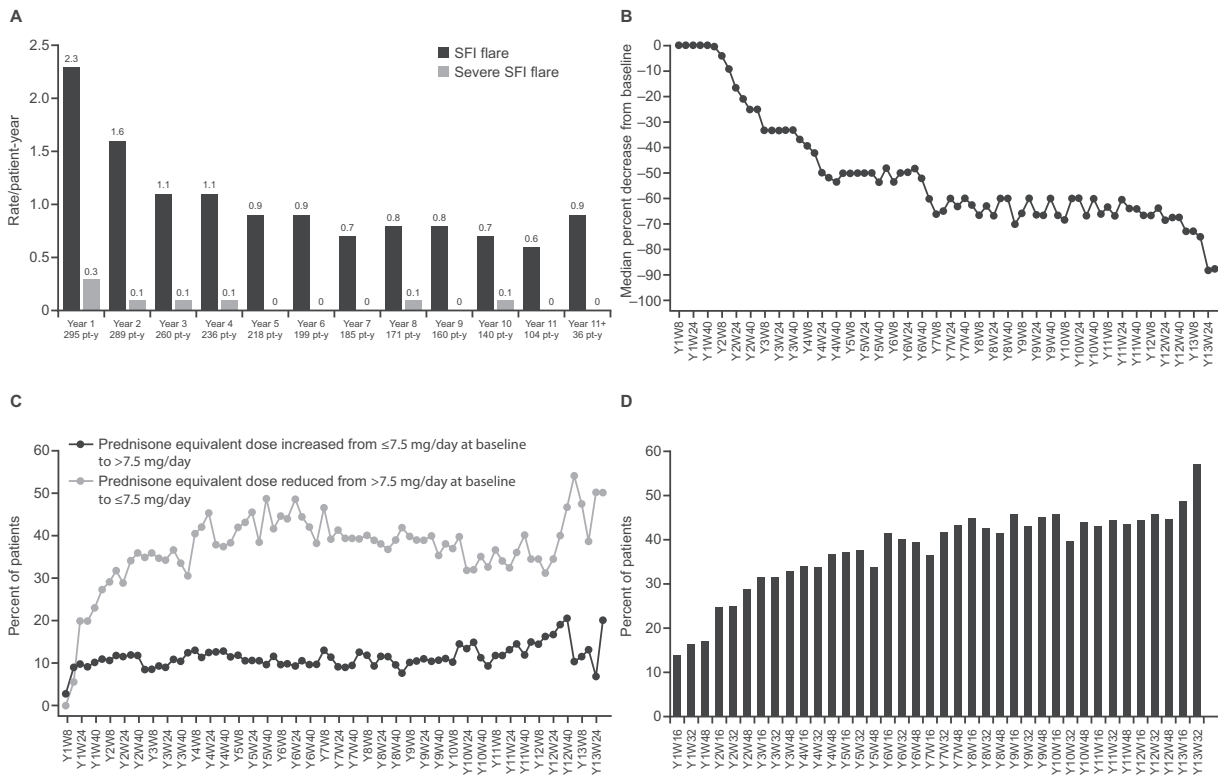
Figure 4. **A**, Rates of all flares and severe flares according to the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) version of the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) Flare Index (SFI). **B**, Median percentage change in prednisone dose from baseline. **C**, Percentage of patients with a prednisone dose increase from ≤7.5 mg/day or a reduction from >7.5 mg/day. **D**, Percentage of patients with low disease activity, defined as a SELENA-SLEDAI score ≤2 and prednisone dose ≤5 mg/day. pt-y = patient-years; W = week; Y = year.

24, 21.1% [42 of 199 patients]) or a severe SFI flare (week 8, 2.7% [6 of 219 patients]; week 24, 3.0% [6 of 199 patients]) remained stable between the follow-up time points.

Biomarkers. Anti-dsDNA autoantibody levels decreased in the serum of patients who were considered anti-dsDNA positive at baseline (Figure 2B), and of the 152 patients with levels above the upper limit of normal at baseline, the anti-dsDNA antibody levels returned to normal in 23 patients (15.1%) and remained normal during the study. Complement levels increased in the serum of patients who had low levels at baseline (Figures 2C and D). Of the 88 patients with low serum C3 levels and the 116 patients with low serum C4 levels at baseline, the levels normalized in 7 patients (8.0%) and 14 patients (12.1%), respectively, and remained normal during the study.

DISCUSSION

This study provides up to 13 years of data on the safety and efficacy of belimumab plus SOC therapy for the treatment of SLE. That approximately one-third of patients continued to receive belimumab for at least 10 years is extraordinary, particularly in light of the rates of adherence to other medications used for and studied in SLE (12). Few patients withdrew due to a lack

of efficacy, and the long-term safety profile of belimumab was acceptable.

The rates and nature of AEs were consistent with the known safety profile of belimumab (4–6,8,9,13,14), and there was no increase in AEs over time. The rate of self-injury/suicide remained low throughout this study and was similar to that reported for the open-label extension of the phase III studies, which investigated the safety of belimumab for up to 6 years in nearly 1,000 patients (13). The incidence of death was 2.7% (0.3 per 100 patient-years); this compares with a mortality rate of 1.1% reported until year 6 in the continuation of the phase III studies (13). Other SLE studies have reported higher rates of mortality than this study; for example, a multinational study of 9,547 patients with an average follow-up of 8.1 years reported a 13.1% incidence of death (15), and a study in the US estimated a 10-year mortality rate of 26% in patients with SLE compared with 19% in matched controls (16). The relatively low incidence of death in the present study is likely related to the exclusion of patients with active lupus nephritis or central nervous system disease (4), but the steroid-sparing effect and/or lower rate of organ damage accrual associated with belimumab might also be a contributing factor (13,14,17).

Consistent with the findings from previous studies (14), there was an increase in the percentage of patients with low serum IgG levels; however, the incidence of infections remained stable.

Sporadic cases of PML have been reported in patients with SLE (18), but rarely in those receiving belimumab (19). In this study, there were no reported cases of PML; however, the study was not powered to assess PML incidence. Although it is likely that all immunosuppressants increase the risk of PML in patients with SLE (20), this seems to remain a rare event, and there is currently no evidence to suggest that belimumab further increases the risk.

As patient withdrawals occurred over time, there was an increase in the percentage of patients who achieved an SRI response. Although it is unlikely that patients with active disease might respond better to belimumab after a year or more of not responding to treatment, another way to examine response rates is to consider the risk of flare in patients who may have already responded. The rates of all SFI flares and severe SFI flares were highest in the first year of the study; from year 5, the flare rates were consistently low, indicating that patients who benefit from belimumab can maintain stable disease. Throughout the study, those patients remaining had reduced requirements for glucocorticoids, and the percentage achieving low disease activity increased. Furthermore, patients continued to have serologic improvements. These findings support the likelihood of sustained, long-term efficacy of belimumab in patients who respond to treatment.

During the 24-week follow-up period after study discontinuation, disease activity remained stable, with little change in the percentages of the population who achieved an SRI response, experienced SFI flares, or had changes in prednisone dose. Longer-term studies with controls are required to fully investigate the effects of discontinuing belimumab, because many factors may affect this, including duration of belimumab exposure, disease severity at discontinuation, possible selection bias in those who returned for follow-up visits, and changes in SOC.

This study had several limitations. Because it was an open-label study with no placebo-controlled arm, and the SOC therapies varied, no treatment comparison can be made. Therefore, the results cannot be unequivocally attributed to belimumab.

In the double-blind phase of the study, some patients initially received lower doses of belimumab before switching to the licensed 10 mg/kg dose. In this analysis, the doses were pooled, given that there were no significant differences observed in the AE profile between the 3 doses in phase II (4). Patients had 1 year of acceptable response to treatment with placebo or belimumab plus SOC therapy before beginning open-label treatment with belimumab; this resulted in patients having more stable disease at the time of entering into the continuation study. Baseline for all patients was the assessment prior to the first dose of belimumab; therefore, the first year reported for this study was double-blind exposure for patients randomized to receive belimumab, and open-label exposure for patients randomized to receive placebo. Not surprisingly, patients who received placebo in the double-blind phase and still qualified as stable enough to continue had lower baseline disease activity compared with patients who received belimumab throughout (data not shown).

Patients who remained in the study were likely to be those who responded better or tolerated belimumab better than patients who withdrew; hence, the findings may not be representative of all patients with SLE. However, the population who entered the continuation study had similar baseline demographics as that in the double-blind study population (4,9). For the large percentage of patients who remained in the study (70.1% at 5 years, 60.1% at 7 years, and 44.3% at 10 years), the results suggest that patients who initially respond to belimumab and continue to receive treatment are likely to experience long-term benefits with continued or improved disease control.

In conclusion, this study describes the long-term safety and efficacy of belimumab in patients with SLE. It is the longest study of belimumab to date, with a high percentage of patients receiving treatment for >10 years. This study provides further safety and efficacy data that are consistent with the data from the phase III long-term extension studies. It will be important to investigate the effects of stopping belimumab in patients who have achieved stable, long-term low-level disease activity; a study (ClinicalTrials.gov identifier NCT02119156) is under way to investigate this question.

AUTHOR CONTRIBUTIONS

ROLE OF THE STUDY SPONSORS

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