Arthritis & Rheumatology
Vol. 74, No. 1, January 2022, pp 112–123
DOI 10.1002/art.41900

American College of Rheumatology
Empowering Rheumatology Professionals

Phase III/IV, Randomized, Fifty-Two–Week Study of the Efficacy and Safety of Belimumab in Patients of Black African Ancestry With Systemic Lupus Erythematosus

Ellen Ginzler,[1] Luiz Sergio Guedes Barbosa,[2] David D'Cruz,[3] Richard Furie,[4] Kathleen Maksimowicz-McKinnon,[5] James Oates,[6] Mittermayer Barreto Santiago,[7] Amit Saxena,[8] Saira Sheikh,[9] Damon L. Bass,[10] Susan W. Burriss,[10] Jennifer A. Gilbride,[11] James G. Groark,[10] Michelle Miller,[10] Amy Pierce,[12] David A. Roth,[10] and Beulah Ji[13]

Objective. Enrollment of patients of Black African ancestry with systemic lupus erythematosus (SLE) in phase II and phase III of the belimumab trials was not reflective of the racial distribution observed in the lupus population. This study was undertaken to assess the efficacy and safety of intravenous (IV) belimumab plus standard therapy in patients of self-identified Black race.

Methods. EMBRACE (GSK Study BEL115471; ClinicalTrials.gov identifier: NCT01632241) was a 52-week multicenter, double-blind, placebo-controlled trial in adults of self-identified Black race with active SLE who received monthly belimumab 10 mg/kg IV, or placebo, plus standard therapy. The optional 26-week open-label extension phase included patients who completed the double-blind phase. The primary end point of the study was SLE Responder Index (SRI) response rate at week 52 with modified proteinuria scoring adapted from the SLE Disease Activity Index 2000 (SLEDAI-2K) (SRI–SLEDAI-2K). Key secondary end points included SRI response rate at week 52, time to first severe SLE flare, and reductions in prednisone dose.

Results. The modified intent-to-treat population comprised 448 patients, of whom 96.9% were women and the mean ± SD age was 38.8 ± 11.42 years. The primary end point (improvement in the SRI–SLEDAI-2K response rate at week 52) was not achieved (belimumab 48.7%, placebo 41.6%; odds ratio 1.40 [95% confidence interval 0.93, 2.11], $P = 0.1068$); however, numerical improvements favoring belimumab were observed, in which the SRI–SLEDAI-2K response rates were higher in those who received belimumab compared with those who received placebo, especially in patients with SLE who had high disease activity or renal manifestations at baseline. The safety profile of belimumab was generally consistent with that observed in previous SLE trials. Adverse events were the primary reasons for double-blind phase withdrawals (belimumab 5.4%, placebo 6.7%).

Conclusion. The primary end point of this study was not achieved, but improvement with belimumab versus placebo was observed, suggesting that belimumab remains a suitable treatment option for SLE management in patients of Black African ancestry.

ClinicalTrials.gov identifier: NCT01632241.

Supported by GlaxoSmithKline (GSK Study BEL115471).

[1]Ellen Ginzler, MD, MPH: State University of New York (SUNY) Downstate Health Sciences University, New York; [2]Luiz Sergio Guedes Barbosa, MD: Núcleo de Terapia Especializada em Cancerologia (NUTEC), Cuiaba, Brazil; [3]David D'Cruz, MD: Guy's Hospital, London, UK; [4]Richard Furie, MD: Northwell Health, Great Neck, New York; [5]Kathleen Maksimowicz-McKinnon, DO: Henry Ford Health System, Detroit, Michigan; [6]James Oates, MD: Medical University of South Carolina and Ralph H. Johnson VA Medical Center, Charleston, South Carolina; [7]Mittermayer Barreto Santiago, MD: Escola Bahiana de Medicina e Saúde Pública, Salvador Bahia, Brazil; [8]Amit Saxena, MD: NYU Grossman School of Medicine, New York; [9]Saira Sheikh, MD: University of North Carolina, Chapel Hill; [10]Damon L. Bass, DO, Susan W. Burriss, MSc, James G. Groark, MD, Michelle Miller, MSc, David A. Roth, MD: GlaxoSmithKline, Collegeville, Pennsylvania; [11]Jennifer A. Gilbride, MSc: GlaxoSmithKline, Stevenage, UK; [12]Amy Pierce, BS: ViiV Healthcare, Research Triangle, North Carolina; [13]Beulah Ji, MD: GlaxoSmithKline, Uxbridge, UK.

Dr. Ginzler has received consulting fees from Janssen (less than $10,000) and grant support from GlaxoSmithKline, Aurinia, and Genentech. Dr. D'Cruz has received consulting fees and/or honoraria from GlaxoSmithKline. Dr. Furie has received consulting fees from GlaxoSmithKline (less than $10,000) and grant support from GlaxoSmithKline. Dr. Maksimowicz-McKinnon has received consulting fees and/or honoraria from ChemoCentryx (less than $10,000). Dr. Saxena has received consulting fees from GlaxoSmithKline, Bristol Myers Squibb, and AstraZeneca (less than $10,000 each). Dr. Sheikh has received consulting fees from GlaxoSmithKline (less than $10,000) and has received grant support from Pfizer. Ms. Pierce owns stock or stock options in GlaxoSmithKline. Drs. Bass, Groark, Roth, and Ji and Mses. Burriss, Gilbride, and Miller own stock or stock options in GlaxoSmithKline. No other disclosures relevant to this article were reported.

Address correspondence to Damon L. Bass, DO, 1250 South Collegeville Road, Collegeville, PA 19426. Email: damon.l.bass@gsk.com.

Submitted for publication December 3, 2020; accepted in revised form June 10, 2021.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that affects multiple organs, including skin, joints, heart, lungs, and kidney (1,2). Black African ancestry is associated with a higher prevalence of SLE, greater disease severity, an increased risk of cardiovascular events, more end-organ damage, and higher mortality rates, compared with a White racial background (3–10).

Belimumab is a human monoclonal antibody that binds to and inhibits the biologic activity of the B lymphocyte stimulator, which plays a key role in B cell selection and differentiation (11,12). The efficacy and safety of intravenous (IV) and subcutaneous belimumab have been demonstrated in phase II and III studies of SLE (13–16). Due to underrepresentation of patients of Black African ancestry in these trials, underpowered subgroup analyses of this population yielded conflicting efficacy data between the phase II and III studies. Post hoc analysis of the phase II study data demonstrated an improved Safety of Estrogens in Lupus Erythematosus National Assessment version of the SLE Disease Activity Index (SELENA–SLEDAI) response in patients of Black African ancestry who received belimumab compared with those who received placebo (17). In contrast, post hoc analysis of pooled data from 2 pivotal phase III studies showed that patients of Black African ancestry had a higher SLE Responder Index (SRI) response rate at week 52 with placebo compared with belimumab (18).

The 52-week EMBRACE study investigated the efficacy and safety of belimumab 10 mg/kg IV plus standard therapy compared with placebo plus standard therapy in adults with SLE of self-identified Black race. This report presents results of the efficacy and safety end point analyses from data collected up to the week 52 visit of the double-blind phase, and the subsequent 24-week open-label extension phase of EMBRACE. Additionally, results presented include subgroup analyses.

PATIENTS AND METHODS

Study design. EMBRACE (GSK Study BEL115471; ClinicalTrials.gov identifier: NCT01632241) was a phase III/IV, multicenter, randomized, double-blind, placebo-controlled, 52-week study (Figure 1) conducted at 88 centers in Brazil, Colombia, France, South Africa, the UK, and the US. The study consisted of a screening phase of up to 5 weeks and a 52-week double-blind phase (date of initiation [first patient's first visit] February 19, 2013; date of double-blind end point analysis June 18, 2018), followed by an optional 6-month open-label extension phase.

Patients. Full selection criteria are provided in the Supplementary Material (available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41900/abstract). Briefly, for inclusion in the double-blind phase, patients had to be age ≥18 years and of self-identified Black race, with a SELENA–SLEDAI score of ≥8 at the time of screening and positivity for antinuclear antibodies (titer ≥1:80 and/or anti–double-stranded DNA [≥30 IU/ml]). Key exclusion criteria included previous treatment with belimumab, severe lupus kidney disease or active nephritis, or central nervous system lupus.

All patients provided written informed consent prior to enrollment. Approval was obtained for all study sites from the ethics committee or institutional review board (IRB) (IRB HGS1006-C1112/tracking QUI1-12-249). The study was conducted in accordance with the ethics principles of the Declaration of Helsinki (19), the International Council for Harmonisation Guidelines for Good Clinical Practice, and any applicable country-specific regulatory

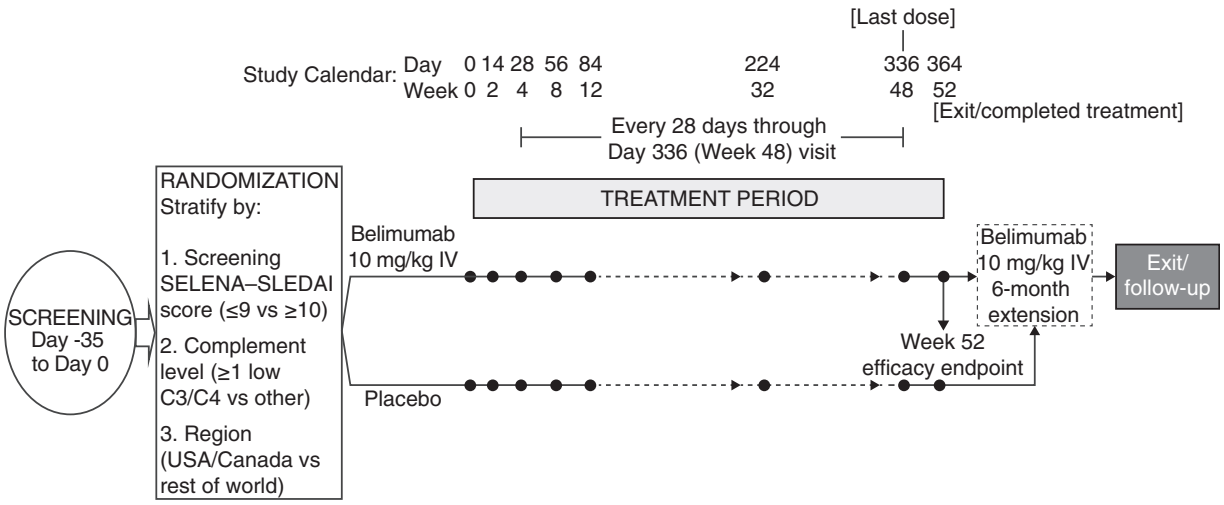

Figure 1. Study design. SELENA–SLEDAI = Safety of Estrogens in Lupus Erythematosus National Assessment–Systemic Lupus Erythematosus Disease Activity Index; IV = intravenous.

requirements. The reporting of this study conforms to the Consolidated Standards of Reporting Trials 2010 guidelines (20).

Randomization and treatment. Using an interactive voice/web response system, patients receiving standard therapy were randomized 2:1 to receive either belimumab 10 mg/kg IV or placebo, which was administered on days 0, 14, and 28 and every 28 days thereafter up to week 48, with a final evaluation at week 52. Randomization was stratified by screening SELENA–SLEDAI score (≤9 versus ≥10), region (US/Canada versus rest of world), and complement level (≥1 test finding showing low C3/C4 [less than the lower limit of normal] versus C3/C4 other [the lower limit of normal or above]). Detailed randomization data are provided in Supplementary Material (http://onlinelibrary.wiley.com/doi/10.1002/art.41900/abstract).

Patients who successfully completed the initial 52-week double-blind phase could enter an optional 6-month open-label extension phase, during which they received belimumab 10 mg/kg IV every 28 days plus standard therapy, irrespective of their previous study assignment. The first dose was given at the week 52 (day 364) visit of the double-blind period (day 1 of the open-label extension phase). Patients who completed the 52-week double-blind phase, but did not enter the 6-month open-label extension phase, were required to return for an additional follow-up visit 8 weeks after their last dose. Patients who withdrew early were required to return for an exit visit 4 weeks after their last dose and a follow-up visit 8 weeks after their last dose.

The original protocol plan was to randomize 816 patients, providing ≥90% power to detect ≥12% absolute improvement in the SRI response rate in the belimumab group compared with the placebo group at a 5% significance level. Due to enrollment challenges, a revised sample size was calculated to include 501 patients (≥334 patients in the belimumab group and ≥167 patients in the placebo group). This sample size provided ≥90% power to detect a minimum 15.55% absolute improvement in SRI–SLEDAI-2K response rate in the belimumab group relative to the placebo group at a 5% significance level (based on the pooled data from efficacy studies BEL112341 and BEL113750) (15,21). These calculations assumed a placebo response rate of 43.95% at week 52.

Study end points and assessments. The primary efficacy end point was the SRI–SLEDAI-2K response rate (defined in the Supplementary Material) at week 52 of the double-blind phase. Unlike in the phase II and phase III studies, the SRI–SLEDAI-2K was selected because of the simplification it offers in proteinuria assessment as compared with the SELENA–SLEDAI proteinuria component; both are clinically meaningful (22). The primary efficacy end point for the open-label extension phase was SRI–SLEDAI-2K response rate at open-label extension week 24. If the open-label extension week 24 data were missing, data from the open-label extension week 28/exit visit were used. This time point is referred to as "open-label extension week 24" throughout the text. Data related to the primary efficacy end point, e.g., the response rate over time, percentage of patients with a durable SRI–SLEDAI-2K response from week 44 through week 52, time to first SRI–SLEDAI-2K response that was maintained through week 52, and duration of longest SRI–SLEDAI-2K response among patients with ≥1 SRI–SLEDAI-2K responses were summarized.

The key secondary end points were SRI–SELENA–SLEDAI at week 52 (open-label extension week 24), time to first severe SLE flare (measured by the SELENA–SLEDAI flare index [SFI]), and proportion of patients whose average prednisone dose had been reduced by ≥25% from baseline to ≤7.5 mg/day during week 40 through week 52 (open-label extension week 28/exit visit), in patients receiving >7.5 mg/day at baseline. Key renal end points included time to first renal flare over 52 weeks and over 28 weeks in the open-label extension, SELENA–SLEDAI–SLEDAI-2K renal domain improvement at week 52, SELENA–SLEDAI–SLEDAI-2K renal domain worsening at week 52, percentage reduction in proteinuria by visit and at week 52 and open-label extension week 24 and week 28/exit visit among those with baseline proteinuria >0.5 gm/24 hours, and proteinuria shift at week 52 and open-label extension week 24 and week 28/exit visit among those with baseline proteinuria >0.5 gm/24 hours. Renal flare is defined in the Supplementary Material (http://onlinelibrary.wiley.com/doi/10.1002/art.41900/abstract).

Biomarkers measured included percentage changes in serum IgG level, anti-dsDNA antibody level (in those who were anti-dsDNA positive [≥30 IU/ml] at baseline), and complement (C3 and C4) levels from baseline. Safety was evaluated by monitoring adverse events (AEs), serious AEs (SAEs), AEs of special interest, vital signs, clinical laboratory test results, and immunogenicity up to 8 weeks posttreatment and throughout the open-label extension phase.

Data analyses. For the double-blind phase, safety analyses were performed on the safety population, defined as all patients who were randomized and treated with at least 1 dose of investigational product. Data on the safety population were summarized according to the treatment the patient was randomized to receive rather than by the treatment that was received, but both were the same for this study. Efficacy analyses were performed on the modified intent-to-treat (ITT) population, defined as the safety population minus those patients who had any assessment at any of 3 study sites that were excluded from the efficacy analyses before the database lock because of potential Good Clinical Practice noncompliance.

For analysis of the primary and 3 key secondary efficacy end points, a step-down sequential testing procedure was used as described in the Supplementary Material. The following subgroup analyses were performed for the primary analysis (SRI–SLEDAI-2K response at week 52): region (US/Canada versus rest of

world), baseline SELENA–SLEDAI–SLEDAI-2K score (≤9 versus ≥10), baseline anti-dsDNA antibody level (≥30 IU/ml versus <30 IU/ml), baseline complement levels (≥1 test finding showing low C3/C4 [less than the lower limit of normal] versus C3/C4 other [the lower limit of normal or above]), and baseline complement and anti-dsDNA antibody levels (≥1 test finding showing low C3/C4 and anti-dsDNA ≥30 IU/ml versus C3/C4 other and anti-dsDNA ≥30 IU/ml). The odds of an SRI–SLEDAI-2K response with belimumab treatment versus placebo were estimated using logistic regression analysis.

For the open-label extension phase, all patients received belimumab, no formal statistical hypothesis testing was completed, and all analyses using descriptive statistics were exploratory in nature. Safety analyses were performed on the ITT population, defined as all randomized patients who received ≥1 dose of treatment (i.e., at double-blind week 52/open-label extension day 1 or a later open-label extension visit). Efficacy analyses were performed on the open-label extension modified ITT population, excluding the same patients as described above for the modified ITT population in the double-blind phase.

Data availability. Anonymized individual participant data and study documents can be requested for further research at http://www.clinicalstudydatarequest.com.

RESULTS

Patient population. In total, 503 patients were randomized, of whom 496 received at least 1 dose of investigational product (safety population), and 448 comprised the modified ITT population that was included in the efficacy analyses. Three hundred forty-five patients in the modified ITT population completed the 52-week double-blind phase; 334 entered the open-label extension phase, and 313 completed the 6-month open-label

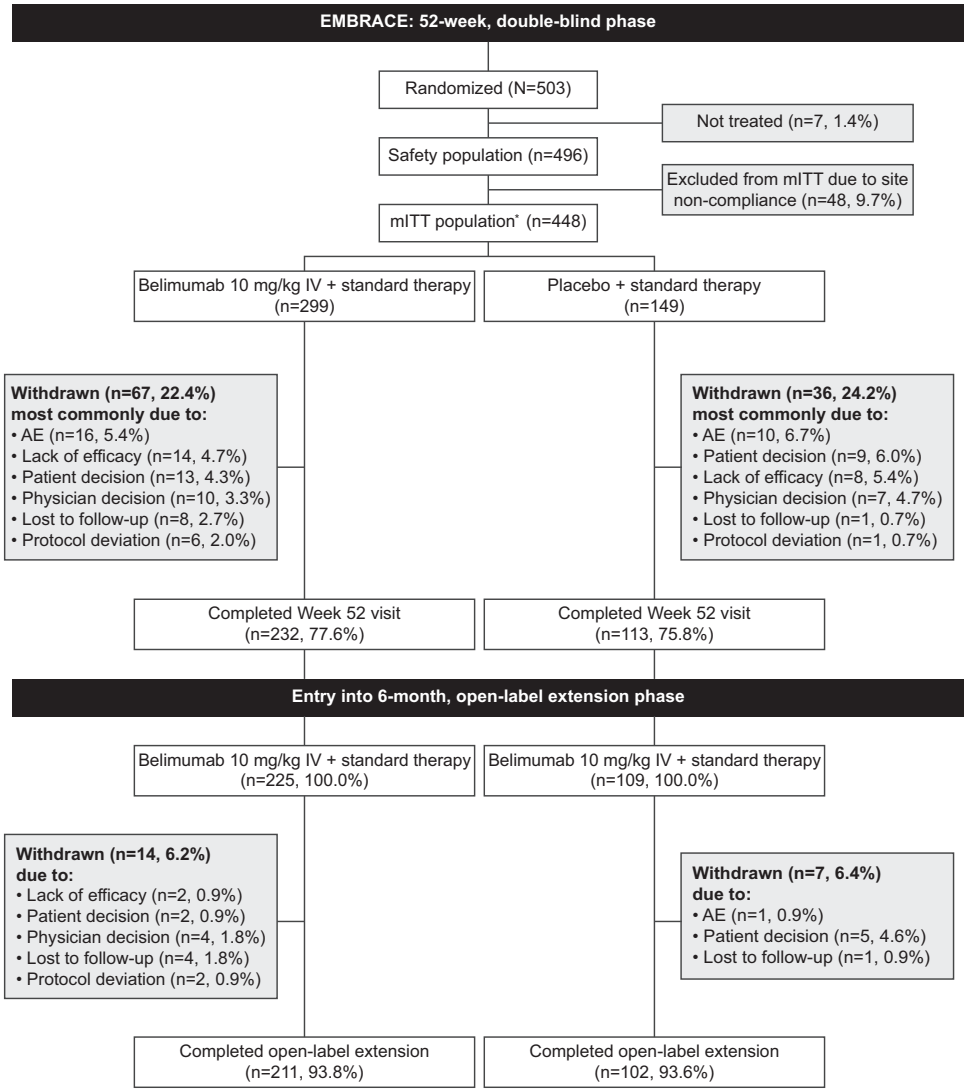

Figure 2. Flow chart of patient disposition. * The modified intent-to-treat (mITT) population consisted of all patients who were randomized and received ≥1 dose of the study agent (48 patients were excluded from efficacy analyses due to noncompliance). IV = intravenous; AE = adverse event.

extension phase (Figure 2). The most frequent reasons for withdrawal in the double-blind safety population were AEs (5.8%), patient decision (4.8%), and lack of efficacy (4.8%). In the open-label extension modified ITT population, study closure/termination due to noncompliance at the aforementioned 3 study sites was the main reason for withdrawal (2.8%), followed by patient decision (1.9%), physician decision, and lost to follow-up (both 1.4%).

Patient demographics and baseline characteristics of the modified ITT population were generally similar between treatment groups and were representative of this type of study design (Table 1 and Supplementary Table 1, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41900/abstract). In the double-blind phase, patients had a mean ± SD age of 38.8 ± 11.4 years, 7 patients (1.6%) were age ≥65 years, and 96.9% were women.

Baseline disease activity was similar between treatment groups (Table 1), except for a slightly lower percentage of patients in the placebo group with ≥1 British Isles Lupus Assessment Group A organ domain involvement (23) (belimumab 17.4%,

Table 1. Patient demographics and baseline characteristics in the modified ITT population*

	Double-blind phase		Open-label extension phase	
	Belimumab, 10 mg/kg IV (n = 299)	Placebo (n = 149)	Continuous belimumab, 10 mg/kg IV (n = 225)	Placebo-to-belimumab, 10 mg/kg IV (n = 109)
Female	290 (97.0)	144 (96.6)	219 (97.3)	107 (98.2)
Age, mean ± SD years	38.6 ± 11.1	39.3 ± 12.2	39.4 ± 10.6	41.6 ± 12.1
Race				
Black African ancestry or African American	293 (98.0)	143 (96.0)	220 (97.8)	103 (94.5)
Multiple	6 (2.0)	6 (4.0)	5 (2.2)	6 (5.5)
Region				
US/Canada	131 (43.8)	65 (43.6)	96 (42.7)	44 (40.4)
Rest of world	168 (56.2)	84 (56.4)	129 (57.3)	65 (59.6)
BMI, mean ± SD kg/m^2	29.46 ± 7.38†	28.97 ± 6.96‡	29.48 ± 7.09§	29.62 ± 7.02¶
SLE disease duration, mean ± SD years#	7.3 ± 7.08**	6.9 ± 7.38	7.5 ± 7.29	8.2 ± 8.03
BILAG organ domain involvement††				
≥1A or 2B	215 (71.9)	107 (71.8)	170 (75.6)	25 (22.9)
≥1A	52 (17.4)	16 (10.7)	42 (18.7)	5 (4.6)
≥1B	273 (91.3)	140 (94.0)	204 (90.7)	51 (46.8)
No A or B	14 (4.7)	4 (2.7)	10 (4.4)	56 (51.4)
SELENA–SLEDAI category				
≤9	146 (48.8)	59 (39.6)	109 (48.4)	87 (79.8)
10–11	77 (25.8)	46 (30.9)	56 (24.9)	9 (8.3)
≥12	76 (25.4)	44 (29.5)	60 (26.7)	13 (11.9)
SELENA–SLEDAI, mean ± SD	9.9 ± 3.52	10.2 ± 2.90	9.9 ± 3.31	5.5 ± 4.20
SELENA–SLEDAI–SLEDAI-2K category				
≤9	141 (47.2)	56 (37.6)	106 (47.1)	86 (78.9)
10–11	74 (24.7)	45 (30.2)	53 (23.6)	9 (8.3)
≥12	84 (28.1)	48 (32.2)	66 (29.3)	14 (12.8)
SELENA–SLEDAI–SLEDAI-2K score, mean ± SD	10.2 ± 3.68	10.5 ± 3.08	10.2 ± 3.52	5.7 ± 4.20
≥1 test finding of low C3/C4	108 (36.1)	57 (38.3)	79 (35.1)	34 (31.2)
Anti-dsDNA ≥30 IU/ml	181 (60.5)	99 (66.4)	135 (60.0)	63 (57.8)
≥1 test finding of low C3/C4 and anti-dsDNA ≥30 IU/ml	91 (30.4)	50 (33.6)	66 (29.3)	30 (27.5)
Renal involvement (SLEDAI-2K organ domain)	55 (18.4)	34 (22.8)	39 (17.3)	21 (19.3)
Proteinuria >0.5 gm/24 hours	53 (17.7)	33 (22.1)	37 (16.4)	22 (20.2)
Average prednisone equivalent dose				
0 mg/day	53 (17.7)	22 (14.8)	–	–
0–7.5 mg/day	62 (20.7)	32 (21.5)	–	–
>7.5 mg/day	184 (61.5)	95 (63.8)	–	–

(Continued)

Table 1. (*Cont'd*)

	Double-blind phase		Open-label extension phase	
	Belimumab, 10 mg/kg IV (n = 299)	Placebo (n = 149)	Continuous belimumab, 10 mg/kg IV (n = 225)	Placebo-to-belimumab, 10 mg/kg IV (n = 109)
Prednisone dose, mean ± SD mg/day	12.1 ± 10.71	12.2 ± 9.95	–	–
Patients receiving treatment				
Steroids	246 (82.3)	127 (85.2)	–	–
Antimalarials	237 (79.3)	124 (83.2)	–	–
Immunosuppressants	167 (55.9)	88 (59.1)	–	–
Aspirin	40 (13.4)	33 (22.1)	–	–
NSAIDs	62 (20.7)	20 (13.4)	–	–
Steroids, immunosuppressants, and antimalarials	113 (37.8)	58 (38.9)	–	–
Steroids and antimalarials only	84 (28.1)	45 (30.2)	–	–
Steroids and immunosuppressants only	28 (9.4)	18 (12.1)	–	–
Steroids only	21 (7.0)	6 (4.0)	–	–
Antimalarials only	25 (8.4)	10 (6.7)	–	–
Immunosuppressants and antimalarials only	15 (5.0)	11 (7.4)	–	–
Immunosuppressants only	11 (3.7)	1 (0.7)	–	–

* Except where indicated otherwise, values are the number (%). Low C3/C4 is defined as less than the lower limit of normal (<90 mg/dl for C3 and <10 mg/dl for C4). ITT = intent-to-treat; IV = intravenous; BMI = body mass index; SLE = systemic lupus erythematosus; BILAG = British Isles Lupus Assessment Group; SELENA–SLEDAI = Safety of Estrogens in Lupus Erythematosus National Assessment–SLE Disease Activity Index; SLEDAI-2K = SLE Disease Activity Index 2000; anti-dsDNA = anti–double-stranded DNA; NSAIDs = nonsteroidal antiinflammatory drugs.
† n = 229.
‡ n = 115.
§ n = 176.
¶ n = 83.
# Defined as (treatment start date – SLE diagnosis date +1)/365.25.
** n = 298.
†† Patients may have been included in >1 category.

placebo 10.7%). There were unexpected imbalances in baseline SELENA–SLEDAI scores and SELENA–SLEDAI–SLEDAI-2K scores, with a larger proportion of patients in the belimumab group having SELENA–SLEDAI scores ≤9 (belimumab 48.8%, placebo 39.6%) and SELENA–SLEDAI–SLEDAI-2K scores ≤9 (belimumab 47.2%, placebo 37.6%).

Efficacy results. The SRI–SLEDAI-2K response rate at week 52, the primary efficacy end point of the double-blind phase, was numerically but not statistically greater in the belimumab group (48.7%) compared with the placebo group (41.6%) (odds ratio 1.40 [95% confidence interval 0.93, 2.11], $P = 0.1068$). Over time, the SRI–SLEDAI-2K (or SRI–SELENA–SLEDAI) response rates were consistently greater in the belimumab group compared with the placebo group, starting at week 28 (Supplementary Figures 1A and B, http://onlinelibrary.wiley.com/doi/10.1002/art.41900/abstract). The SRI–SLEDAI-2K response rate at open-label extension week 24, the primary efficacy end point of the open-label extension phase, was 73.6% and 18.8% in the continuous belimumab group and the placebo-to-belimumab group, respectively, since the start of belimumab treatment (i.e., over 76 weeks in the continuous belimumab group and 24 weeks in the placebo-to-belimumab group). Components of the primary end point of the double-blind and open-label extension phases are shown in Figure 3.

A durable SRI–SLEDAI-2K response from week 44 through week 52 was achieved by 126 patients (42.3%) in the belimumab group and 48 patients (32.2%) in the placebo group (odds ratio 1.66 [95% confidence interval 1.08, 2.56], $P = 0.0209$). The 25th percentile of the time to SRI–SLEDAI-2K response maintained until week 52 was 116 days (16.6 weeks) in the belimumab group and 204 days (29.1 weeks) in the placebo group (hazard ratio 1.41 [95% confidence interval 1.04, 1.90], $P = 0.0256$) (Supplementary Figure 2, http://onlinelibrary.wiley.com/doi/10.1002/art.41900/abstract). The mean ± SD duration of longest SRI–SLEDAI-2K response among patients with ≥1 response was longer in the belimumab group (172.9 ± 115.65 days [24.7 weeks]) compared with the placebo group (139.1 ± 110.08 days [19.9 weeks]), resulting in an adjusted treatment difference of 40.10 days (95% confidence interval 14.74, 65.46, $P = 0.0020$).

Since the primary end point did not meet statistical significance, key secondary end points in the prespecified sequence (SRI–SELENA–SLEDAI response, time to first severe SFI flare, and prednisone use) could not be declared as statistically significant. The percentage of SRI–SELENA–SLEDAI responders is presented in the Supplementary Material and in Supplementary

Figure 1B (http://onlinelibrary.wiley.com/doi/10.1002/art.41900/abstract). The SELENA–SLEDAI–SLEDAI-2K change from baseline over time is shown in Supplementary Figure 3 (http://onlinelibrary.wiley.com/doi/10.1002/art.41900/abstract).

Over the 52-week double-blind phase, patients in the belimumab group had a 23% lower risk of experiencing a severe SFI flare than those in the placebo group (hazard ratio 0.77 [95% confidence interval 0.51, 1.17], $P = 0.2264$). Among patients experiencing a severe SFI flare (58 of 299 [19.4%] in the belimumab group; 37 of 149 [24.8%] in the placebo group), the median time to first severe SFI flare was similar between the belimumab and placebo groups (study day 176 in the belimumab group versus study day 175 in the placebo group). During the open-label extension phase, 4.0% of patients (9 of 225) and 5.5% of patients (6 of 109) in the continuous belimumab and placebo-to-belimumab groups, respectively, experienced a severe SFI flare.

There was no forced steroid tapering in this study. At baseline, 279 patients (modified ITT population; 184 in the belimumab group and 95 in the placebo group) received prednisone at >7.5 mg/day. Of these patients, 27 (14.7%) in the belimumab group and 12 (12.6%) in the placebo group achieved a reduction in prednisone dose by ≥25% from baseline to ≤7.5 mg/day during week 40 to week 52 of the double-blind phase (odds ratio 1.30 [95% confidence interval 0.61, 2.80], $P = 0.4996$). In the open-

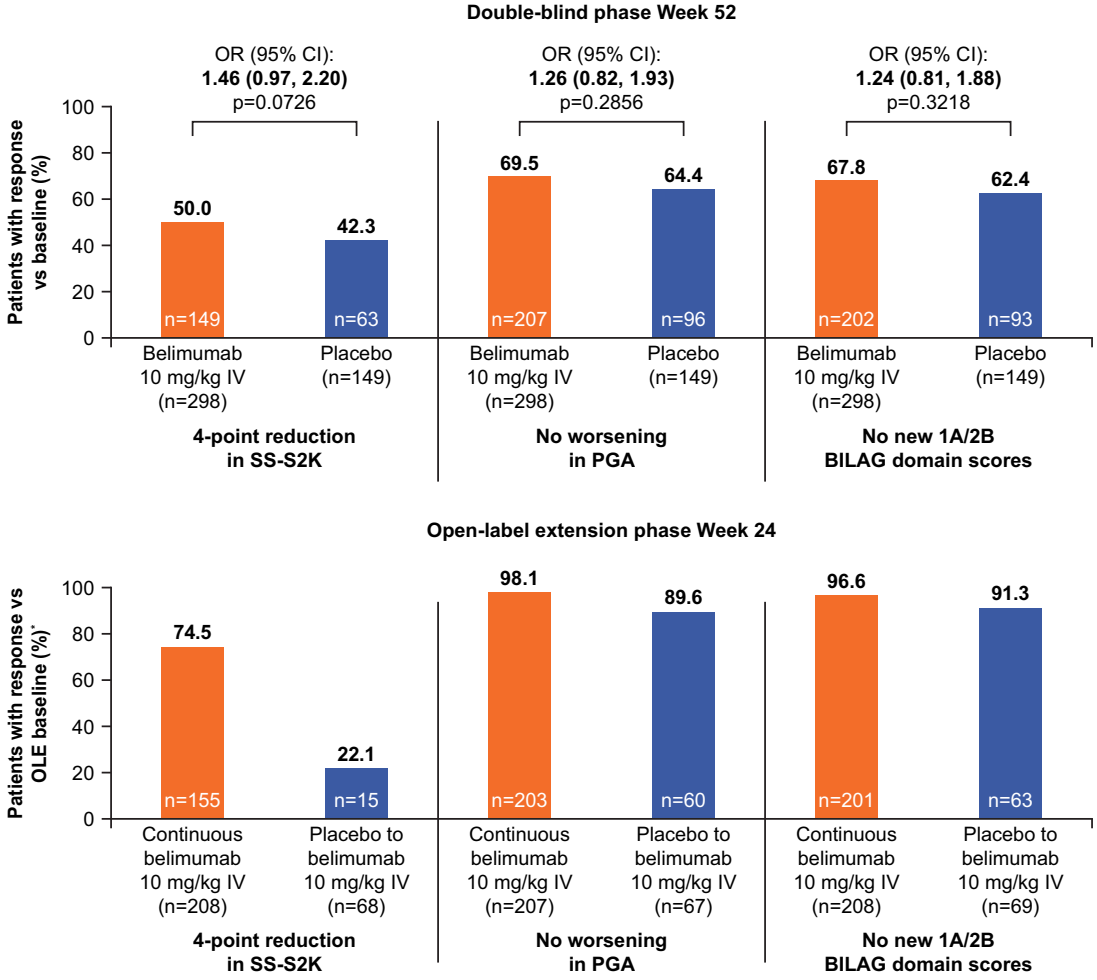

Figure 3. Response rates based on the 3 individual components of the Systemic Lupus Erythematosus (SLE) Responder Index–SLE Disease Activity Index 2000 (SLEDAI-2K) response, with modified SLEDAI scoring for proteinuria, at week 52 of the double-blind phase and at week 24 of the open-label extension (OLE) phase in the modified intent-to-treat population. Odds ratios (ORs) with 95% confidence intervals (95% CIs) and *P* values were derived using a logistic regression model to compare belimumab with placebo, with covariates of treatment group, baseline Safety of Estrogens in Lupus Erythematosus National Assessment–SLEDAI (SELENA–SLEDAI)–SLEDAI-2K (SS-S2K) score (≤9 versus ≥10), baseline complement levels (≥1 test finding showing low C3/C4 [less than the lower limit of normal] versus C3/C4 other [the lower limit of normal or above]), and region (US/Canada versus rest of world). The open-label extension phase used observed data, and the double-blind phase used nonresponder imputation for withdrawals or treatment failures. The OR was not calculated for the open-label extension phase, as no formal hypothesis testing was performed. * Open-label extension baseline (pre-belimumab) was used for the SELENA–SLEDAI–SLEDAI-2K analysis, with modified SLEDAI scoring for proteinuria, of the open-label extension phase. Patients in the continuous belimumab group received belimumab for 18 months, and those in the placebo-to-belimumab group received belimumab for 6 months. IV = intravenous; PGA = physician global assessment; BILAG = British Isles Lupus Assessment Group.

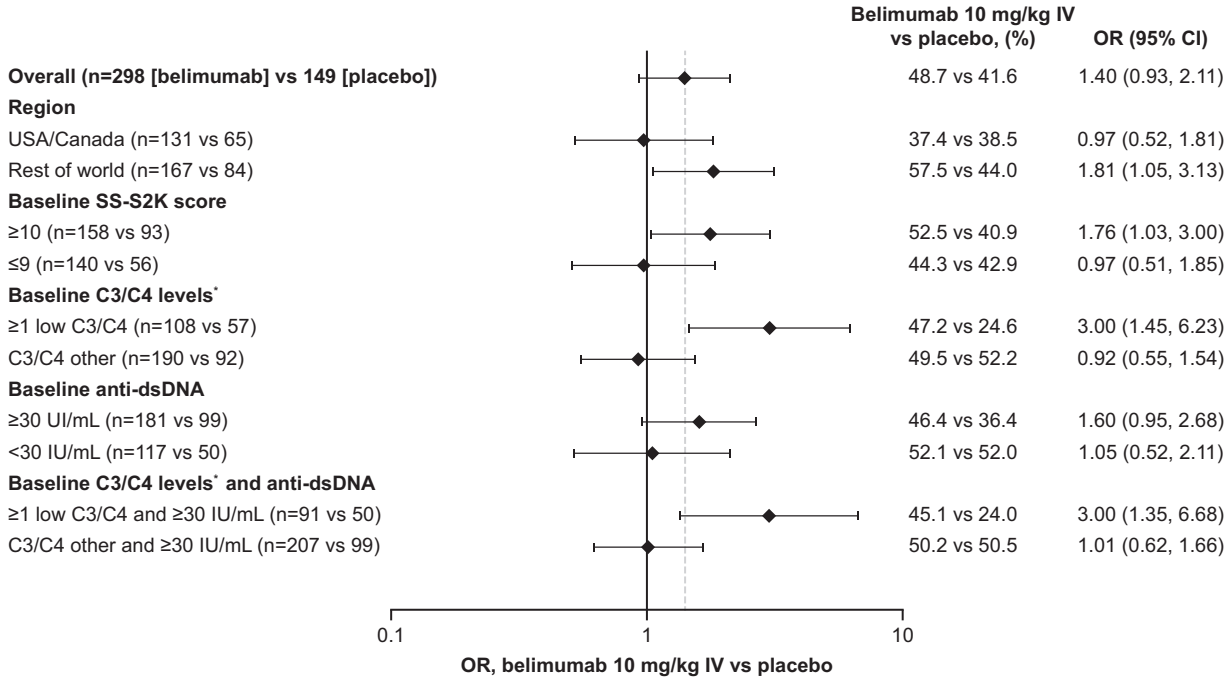

Figure 4. Subgroup analysis of SLE Responder Index–SLEDAI-2K (SS-S2K) response rates at week 52. * Low C3/C4 is defined as C3/C4 levels less than the lower limit of normal (<90 mg/dl for C3 and <10 mg/dl for C4), and C3/C4 other is defined as levels at the lower limit of normal or above. Anti-dsDNA = anti–double-stranded DNA (see Figure 3 for other definitions).

label extension phase, 31.9% of patients (44 of 138) in the continuous belimumab group had achieved a reduction in prednisone dose to ≤7.5 mg/day compared with the start of the double-blind phase, whereas 14.8% of patients (8 of 54) in the placebo-to-belimumab group achieved this compared with the start of the open-label extension phase.

Subgroup analyses revealed that belimumab-treated patients had greater SRI–SLEDAI-2K response rates compared with patients who received placebo if they had the following at baseline: 1) SELENA–SLEDAI–SLEDAI-2K scores ≥10 (52.5% versus 40.9%), 2) positive anti-dsDNA antibody levels (46.4% versus 36.4%), 3) low complement levels (47.2% versus 24.6%), or 4) low complement levels and positive anti-dsDNA (45.1% versus 24.0%) (Figure 4). Patients in the US/Canada had similar SRI–SLEDAI-2K response rates with belimumab as with placebo (37.4% versus 38.5%), whereas those in the rest of the world had a higher response rate with belimumab compared with placebo (57.5% versus 44.0%).

Patients in the double-blind phase who received belimumab had a 46% lower risk of experiencing a renal flare compared with those who received placebo (hazard ratio 0.54 [95% confidence interval 0.21, 1.36], $P = 0.1880$). Among patients who experienced a renal flare (9 of 299 [3.0%] in the belimumab group; 9 of 149 [6.0%] in the placebo group), the median study day of the renal flare was day 196 (range 57–309) in the belimumab group and day 153 (range 30–337) in the placebo group. In the open-label extension phase, 3.1% of patients (7 of 225) in the continuous belimumab group and 4.6% of patients (5 of 109) in the placebo-to-belimumab group experienced renal flares over 28 weeks. Among these patients, the median study day of the renal flare was day 169 (range 162–193) in the continuous belimumab group and day 169 (range 85–197) in the placebo-to-belimumab group.

In the double-blind phase, among patients with baseline SELENA–SLEDAI–SLEDAI-2K renal involvement, more patients in the belimumab group (41.8% [23 of 55]) experienced improvement in this domain compared with those in the placebo group (20.6% [7 of 34]). Among those without baseline SELENA–SLEDAI–SLEDAI-2K renal involvement, the percentage of patients who experienced worsening in this domain was low in both groups (6.1% [15 of 244] in the belimumab group; 7.8% [9 of 115] in the placebo group). Changes in proteinuria by visit in patients in the double-blind phase with baseline proteinuria >0.5 gm/24 hours are shown in Supplementary Figure 4 (http://onlinelibrary.wiley.com/doi/10.1002/art.41900/abstract). The median percentage change in proteinuria at week 52 among patients with baseline proteinuria >0.5 gm/24 hours was numerically greater with belimumab treatment compared with placebo (−65.27% [interquartile range −81.1, −38.8], n = 38 versus −32.89% [interquartile range −76.6, 36.3], n = 23). Among patients with baseline proteinuria >0.5 gm/24 hours in the open-label extension phase, the median percentage change in proteinuria at open-label extension week 24 was −73.99% (interquartile range −91.3, −36.4) in 34 patients receiving continuous belimumab since the start of the double-blind phase and −34.30% (interquartile range −58.8, 29.4) in 17 patients who switched from

Table 2. Summary of treatment-emergent AEs in the safety population*

	Double-blind phase		Open-label extension phase	
	Belimumab, 10 mg/kg IV (n = 331)	Placebo (n = 165)	Continuous belimumab, 10 mg/kg IV (n = 242)	Placebo-to-belimumab, 10 mg/kg IV (n = 117)
Any AE	277 (83.7)	144 (87.3)	152 (62.8)	78 (66.7)
Treatment-related AEs	111 (33.5)	47 (28.5)	36 (14.9)	20 (17.1)
Serious AEs	36 (10.9)	31 (18.8)	13 (5.4)	6 (5.1)
Severe AEs	46 (13.9)	37 (22.4)	9 (3.7)	10 (8.5)
Serious and/or severe AEs	57 (17.2)	46 (27.9)	17 (7.0)	15 (12.8)
AEs resulting in treatment discontinuation	22 (6.6)	12 (7.3)	0	1 (0.9)
Deaths	2 (0.6)	0	0	0

* Values are the number (%). AEs = adverse events; IV = intravenous.

placebo to belimumab at the start of the open-label extension phase. At week 52 of the double-blind phase, 16 patients (42.1%) in the belimumab group and 6 (26.1%) in the placebo group with baseline proteinuria >0.5 gm/24 hours experienced a downward shift in proteinuria to ≤0.5 gm/24 hours. At open-label extension week 24, 20 patients (58.8%) in the continuous belimumab group and 6 (35.3%) in the placebo-to-belimumab group experienced a downward shift in proteinuria to ≤0.5 gm/24 hours since the start of the double-blind phase and the start of the open-label extension phase, respectively.

Biomarker results are shown in Supplementary Table 2 (http://onlinelibrary.wiley.com/doi/10.1002/art.41900/abstract). With belimumab versus placebo treatment in the double-blind phase, there was a greater reduction in the percentage change in IgG levels from baseline ($P < 0.0001$) and percentage change in anti-dsDNA levels from baseline ($P = 0.0004$ among patients who were anti-dsDNA positive at baseline). Greater increases in C3 and C4 levels were observed in those who received belimumab versus those who received placebo ($P = 0.0087$ and $P < 0.0001$, respectively).

Safety. In the double-blind phase, the proportion of patients who experienced at least 1 AE was similar between treatment groups (83.7% in the belimumab group; 87.3% in the placebo group). In the open-label extension phase, the proportion of patients who experienced at least 1 AE was 62.8% and 66.7% in the continuous belimumab and placebo-to-belimumab groups, respectively (Table 2 and Supplementary Table 3, http://onlinelibrary.wiley.com/doi/10.1002/art.41900/abstract).

The AEs most commonly reported in either treatment group during the double-blind phase were upper respiratory tract infection (14.8% in the belimumab group; 8.5% in the placebo group) and urinary tract infection (13.0% in the belimumab; 12.7% in the placebo group). In the open-label extension phase, in which all patients received belimumab, the AEs most commonly reported (occurring in ≥5% of patients) were upper respiratory tract infection (6.7%), influenza (6.4%), and urinary tract infection (5.6%). AEs in the double-blind phase occurring more commonly in belimumab-treated patients compared with placebo-treated patients (and occurring in ≥5% of patients) and with a between-group difference in incidence of ≥1% were upper respiratory tract infection, diarrhea, sinusitis, vomiting, cough, and hypertension.

In the double-blind phase, the incidence of SAEs was lower in the belimumab group (10.9%) compared with the placebo group (18.8%), and the SAE with the highest incidence was infections and infestations (3.3% in the belimumab group; 7.9% in the placebo group). There was a similar incidence of infections and infestations between the belimumab group and placebo group (59.2% and 60.0%, respectively) and a similar incidence of serious infections and serious infestations between the belimumab group and placebo group (3.3% and 7.9%, respectively). The rate of opportunistic infection AEs of special interest, including active tuberculosis and herpes zoster, was 0.6% in the belimumab group and 1.2% in the placebo group. Overall, during the open-label extension phase, 5.3% of patients experienced at least 1 SAE.

In total, 6.6% of patients in the belimumab group and 7.3% in the placebo group discontinued treatment due to an AE in the double-blind phase. In the belimumab group, treatment was discontinued most commonly because of lupus nephritis (0.9%). Two patients in the belimumab group (0.6%) died, and none died in the placebo group. Both deaths were considered not to be related to belimumab by the study investigator. The death in 1 patient was attributable to nosocomial meningitis, secondary to an SAE of severe cerebrovascular accident (76 days after administration of the first dose of belimumab, where there was a possibility that the cerebrovascular accident was due to belimumab). The patient had a history of hypertension and infection. The second patient, who received 1 dose of belimumab and developed multidrug-resistant pneumonia 8 days later, died on day 46. There were no deaths in the open-label extension phase, and 1 patient in the placebo-to-belimumab group experienced an AE that resulted in treatment discontinuation (Table 2). No clinically meaningful differences between treatment groups

were found in the incidence of malignancy, postinfusion reactions, or psychiatric disease.

DISCUSSION

To our knowledge, this is the first randomized, placebo-controlled clinical trial in SLE focusing on patients of self-identified Black race. The response to treatment with belimumab 10 mg/kg IV plus standard therapy did not achieve statistical superiority over placebo plus standard therapy when assessed on the basis of the double-blind phase primary end point; however, SRI–SLEDAI-2K response rates were numerically higher in those who received belimumab. Although the magnitude of the treatment group difference favoring belimumab is lower in this study (response rate 49% with belimumab versus 42% with placebo, odds ratio 1.40 [95% confidence interval 0.93, 2.11]) when compared with that observed in the 2 pivotal phase III studies of IV belimumab (response rate in the Study of Belimumab in Subjects with SLE 52-week trial [BLISS-52], 58% with belimumab versus 44% with placebo, odds ratio 1.83 [95% confidence interval 1.30, 2.59]; response rate in the BLISS 76-week trial [BLISS-76], 43% with belimumab versus 34% with placebo, odds ratio 1.52 [95% confidence interval 1.07, 2.15]), the efficacy results are directionally consistent (13,14,24). Our results support the post hoc analysis of the previous phase II study, which showed an improved SELENA–SLEDAI response with belimumab compared with placebo in patients of Black African ancestry (17) and contradicted the post hoc analyses of the pivotal phase III studies (18,25).

The large difference in SRI–SLEDAI-2K response in the open-label extension phase between the 2 treatment groups may be due to the difference in the length of time that patients received belimumab (>76 weeks in the continuous belimumab group versus 24 weeks in the placebo-to-belimumab group). At open-label extension baseline (start of belimumab treatment), the placebo-to-belimumab group also had lower disease activity compared with the continuous belimumab group, which may have made it more difficult to meet the SLEDAI component of the SRI end point.

The durable SRI–SLEDAI-2K response showed a greater difference between treatment groups relative to that in the primary analysis. The time to first SRI–SLEDAI-2K response that was maintained through week 52 occurred earlier in the belimumab group compared with the placebo group, and the belimumab group had a longer duration of SRI–SLEDAI-2K response compared with the placebo group.

The population recruited in this study had a generally lower disease activity than the overall population in the pivotal phase III studies (13,14,16), which may have contributed to the reduced effect size observed. However, subgroup analyses showed higher SRI–SLEDAI-2K responses in the belimumab group compared with the placebo group among patients with high disease activity at baseline (i.e., SELENA–SLEDAI–SLEDAI-2K score ≥10, low complement levels, and low complement levels plus positive anti-dsDNA). This finding is consistent with subgroup analyses of the pivotal phase III trials, in which patients with high disease activity had a greater SRI–SELENA–SLEDAI effect size with belimumab compared with standard therapy (Supplementary Figure 5, http://onlinelibrary.wiley.com/doi/10.1002/art.41900/abstract) (26). These findings add to the growing body of evidence supporting the benefit of belimumab in patients with high disease activity, regardless of race. High disease activity is more common in those of non-White descent, including African descendants (10), and this classification may be useful to practicing clinicians to more easily identify patients who might have an enhanced response to belimumab.

Regional analyses of the primary end point showed that patients in the rest-of-world subgroup compared with the US/Canada subgroup had a higher response to belimumab than to placebo, while those in the US/Canada subgroup had a similar response between treatment groups. A lower proportion of patients in the US/Canada subgroup had low complement levels at baseline than those in the rest-of-world subgroup. Due to this imbalance of baseline disease activity by region, post hoc analyses for response by region and baseline complement level were performed. In patients with low complement levels in both regions, a benefit was observed with belimumab compared with placebo. These regional baseline differences may have contributed to the higher response difference favoring belimumab in the rest-of-world subgroup compared with the US/Canada subgroup.

Renal involvement is more common and severe in patients of Black African ancestry (10,27–29). Although this study was not powered to determine a treatment difference in renal end points, patients treated with belimumab had an improved SELENA–SLEDAI–SLEDAI-2K renal domain score, decrease in proteinuria, and a downward shift in proteinuria among those with high proteinuria at baseline. In this study, the observation that patients with renal manifestations may benefit from treatment with belimumab is supported by the post hoc analysis performed by Dooley et al and was confirmed in the BLISS in Lupus Nephritis study (ClinicalTrials.gov identifier: NCT01639339), which also included patients of Black African ancestry (30,31).

Immunoglobulin and SLE biomarker responses from this study were consistent with those in the pivotal belimumab studies (13,14). The incidences of AEs, and the AE and SAE profile in this study, were consistent with those in the overall SLE population of the BLISS-52, BLISS-76, and BLISS-SC trials (13,14,16). Although patients in the open-label extension continuous belimumab group received more exposure to belimumab than those in the placebo-to-belimumab group, no clinically meaningful safety differences were observed.

This study has several limitations. The introduction of the SRI–SLEDAI-2K as a treatment response end point was expected to increase the sensitivity of the study to identify a between-group treatment difference as compared with that assessed using the SRI–SELENA–SLEDAI, and consequently, the sample size was

reduced from the original protocol (816 to 501 patients). Unfortunately, the predicted increase in sensitivity was not realized and this, combined with the loss of 48 participants from the modified ITT population due to site noncompliance, resulted in reduced power. Despite stratification at screening, a higher proportion of patients in the belimumab group had a SELENA–SLEDAI–SLEDAI-2K score of ≤9 at baseline, and the mean baseline SELENA–SLEDAI–SLEDAI-2K score was slightly lower compared with the placebo group. It is possible that a 4-point reduction in the score may therefore have been harder to achieve in the belimumab group compared with the placebo group due to disease changes after screening. Furthermore, subgroup analyses across studies have consistently demonstrated that patients with baseline SELENA–SLEDAI scores of ≥10 benefit more from treatment with belimumab compared with those with baseline scores of ≤9 (Supplementary Figure 5, http://onlinelibrary.wiley.com/doi/10.1002/art.41900/abstract). Therefore, this imbalance may have contributed to the reduction in the overall effect size on the primary end point.

This study was initiated as one of the postapproval commitments for belimumab. The decision not to include forced steroid tapering, which was made to ensure the study design was comparable to that of the pivotal BLISS studies, may have contributed to the inability to differentiate between the 2 groups. Although a reduction in steroid use without mandated tapering has been demonstrated following belimumab treatment (32), steroid tapering is an important consideration for the design of future studies in order to ensure that the full treatment effect of a new medicine may be demonstrated. Other than self-identification, no definitions were applied to the inclusion criteria of Black race. This resulted in the inclusion of a proportion of patients who did not identify as being primarily of Black race but considered themselves of mixed race. Although there is variability in the population of patients who self-identified as being of Black race, this study is unique in the SLE field in that it limits the inclusion criteria by race.

Overall, belimumab 10 mg/kg IV plus standard therapy was generally well tolerated; no new safety signals were observed, and findings were consistent with the known safety profile of belimumab. Efficacy and safety appear to be maintained over time. Although statistical significance was not achieved overall, a greater percentage of patients attained the primary end point in the belimumab group compared with the placebo group. Importantly, patients with baseline high disease activity or renal disease benefited from treatment with belimumab, a finding that adds to the growing body of evidence supporting the benefit of belimumab in these groups (13,14,16,30). This study provides clinically meaningful evidence to inform clinicians regarding the management of SLE in patients of Black African ancestry, especially those with high disease activity, a patient population with high unmet needs.

ACKNOWLEDGMENTS

The authors would like to thank Grace Kang (GlaxoSmithKline) for her contribution to this study. They would also like to thank the patients and their families, as well as the investigators and support staff.

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. Ginzler 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. Ginzler, Guedes Barbosa, Santiago, Bass, Burriss, Pierce, Roth, Ji.

Acquisition of data. Ginzler, Guedes Barbosa, D'Cruz, Furie, Maksimowicz-McKinnon, Oates, Santiago, Saxena, Sheikh.

Analysis and interpretation of data. Ginzler, Guedes Barbosa, D'Cruz, Furie, Maksimowicz-McKinnon, Oates, Santiago, Saxena, Sheikh, Bass, Burriss, Gilbride, Groark, Miller, Pierce, Roth, Ji.

ROLE OF THE STUDY SPONSOR

GlaxoSmithKline designed, conducted, and funded this study, contributed to collection, analysis, and interpretation of the data, and supported the authors in development of the manuscript. Medical writing support was provided by Casmira Brazaitis, PhD, of Fishawack Indicia Ltd (Knutsford, UK) and funded by GlaxoSmithKline. All authors, including those employed by GlaxoSmithKline, approved the content of the submitted manuscript. GlaxoSmithKline was involved in the decision to submit the manuscript for publication.

REFERENCES

1. Herrada AA, Escobedo N, Iruretagoyena M, Valenzuela RA, Burgos PI, Cuitino L, et al. Innate immune cells' contribution to systemic lupus erythematosus [review]. Front Immunol 2019;10:772.
2. Menez SP, El Essawy B, Atta MG. Lupus nephritis: current treatment paradigm and unmet needs [review]. Rev Recent Clin Trials 2018;13:105–13.
3. Stojan G, Petri M. Epidemiology of systemic lupus erythematosus: an update [review]. Curr Opin Rheumatol 2018;30:144–50.
4. Barbhaiya M, Feldman CH, Guan H, Gómez-Puerta JA, Fischer MA, Solomon DH, et al. Race/ethnicity and cardiovascular events among patients with systemic lupus erythematosus. Arthritis Rheumatol 2017;69:1823–31.
5. Lewis MJ, Jawad AS. The effect of ethnicity and genetic ancestry on the epidemiology, clinical features and outcome of systemic lupus erythematosus [review]. Rheumatology (Oxford) 2017;56:i67–77.
6. Munroe ME, Vista ES, Merrill JT, Guthridge JM, Roberts VC, James JA. Pathways of impending disease flare in African-American systemic lupus erythematosus patients. J Autoimmun 2017;78:70–8.
7. Rees F, Doherty M, Grainge MJ, Lanyon P, Zhang W. The worldwide incidence and prevalence of systemic lupus erythematosus: a systematic review of epidemiological studies [review]. Rheumatology (Oxford) 2017;56:1945–61.
8. Pons-Estel GJ, Alarcon GS, Scofield L, Reinlib L, Cooper GS. Understanding the epidemiology and progression of systemic lupus erythematosus [review]. Semin Arthritis Rheum 2010;39:257–68.
9. Uribe AG, Alarcon GS. Ethnic disparities in patients with systemic lupus erythematosus [review]. Curr Rheumatol Rep 2003;5:364–9.
10. Gonzalez LA, Toloza SM, McGwin G Jr, Alarcon GS. Ethnicity in systemic lupus erythematosus (SLE): its influence on susceptibility and outcomes. Lupus 2013;22:1214–24.
11. Baker KP, Edwards BM, Main SH, Choi GH, Wager RE, Halpern WG, et al. Generation and characterization of LymphoStat-B, a human

monoclonal antibody that antagonizes the bioactivities of B lymphocyte stimulator. Arthritis Rheum 2003;48:3253–65.

12. Hase H, Kanno Y, Kojima M, Hasegawa K, Sakurai D, Kojima H, et al. BAFF/BLyS can potentiate B-cell selection with the B-cell coreceptor complex. Blood 2004;103:2257–65.
13. Furie R, Petri M, Zamani O, Cervera R, Wallace DJ, Tegzová D, et al. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. Arthritis Rheum 2011; 63:3918–30.
14. Navarra SV, Guzmán RM, Gallacher AE, Hall S, Levy RA, Jimenez RE, et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. Lancet 2011;377:721–31.
15. Zhang F, Bae SC, Bass D, Chu M, Egginton S, Gordon D, et al. A pivotal phase III, randomised, placebo-controlled study of belimumab in patients with systemic lupus erythematosus located in China, Japan and South Korea. Ann Rheum Dis 2018;77:355–63.
16. Stohl W, Schwarting A, Okada M, Scheinberg M, Doria A, Hammer AE, et al. Efficacy and safety of subcutaneous belimumab in systemic lupus erythematosus: a fifty-two–week randomized, double-blind, placebo-controlled study. Arthritis Rheumatol 2017;69:1016–27.
17. Stohl W, Hilbert DM. The discovery and development of belimumab: the anti-BLyS-lupus connection. Nat Biotechnol 2012;30:69–77.
18. Benlysta prescribing information. Philadelphia (PA): GlaxoSmithKline; 2021. URL: https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Benlysta/pdf/BENLYSTA-PI-MG-IFU-COMBINED.PDF.
19. World Medical Association. WMA Declaration of Helsinki: ethical principles for medical research involving human subjects. URL: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/.
20. Schulz KF, Altman DG, Moher D, Group C. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ 2010;340:c332.
21. Doria A, Stohl W, Schwarting A, Okada M, Scheinberg M, van Vollenhoven R, et al. Efficacy and safety of subcutaneous belimumab in anti–double-stranded DNA–positive, hypocomplementemic patients with systemic lupus erythematosus. Arthritis Rheumatol 2018;70:1256–64.
22. Gladman DD, Ibanez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. J Rheumatol 2002;29:288–91.
23. Yee CS, Farewell V, Isenberg DA, Prabu A, Sokoll K, Teh LS, et al. Revised British Isles Lupus Assessment Group 2004 index: a reliable tool for assessment of systemic lupus erythematosus activity. Arthritis Rheum 2006;54:3300–5.
24. Benlysta summary of product characteristics. Phiuladelphia (PA): GlaxoSmithKline; 2021. URL: https://gskpro.com/content/dam/global/hcpportal/en_US/Prescribing_Information/Benlysta/pdf/BENLYSTA-PI-MG-IFU.PDF.
25. US Food and Drug Administration. Belimumab statistical review and evaluation. 2011. URL: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/125370Orig1s000StatR.pdf.
26. Van Vollenhoven RF, Petri MA, Cervera R, Roth DA, Ji BN, Kleoudis CS, et al. Belimumab in the treatment of systemic lupus erythematosus: high disease activity predictors of response. Ann Rheum Dis 2012;71:1343–9.
27. Johnson SR, Urowitz MB, Ibanez D, Gladman DD. Ethnic variation in disease patterns and health outcomes in systemic lupus erythematosus. J Rheumatol 2006;33:1990–5.
28. Feldman CH, Hiraki LT, Liu J, Fischer MA, Solomon DH, Alarcón GS, et al. Epidemiology and sociodemographics of systemic lupus erythematosus and lupus nephritis among US adults with Medicaid coverage, 2000–2004. Arthritis Rheum 2013;65:753–63.
29. Alarcón GS, McGwin G Jr, Petri M, Reveille JD, Ramsey-Goldman R, Kimberly RP, et al. Baseline characteristics of a multiethnic lupus cohort: PROFILE. Lupus 2002;11:95–101.
30. Furie R, Rovin BH, Houssiau F, Malvar A, Teng YK, Contreras G, et al. Two-year, randomized, controlled trial of belimumab in lupus nephritis. N Engl J Med 2020;383:1117–28.
31. Dooley MA, Houssiau F, Aranow C, D'Cruz DP, Askanase A, Roth DA, et al. Effect of belimumab treatment on renal outcomes: results from the phase 3 belimumab clinical trials in patients with SLE. Lupus 2013;22:63–72.
32. Van Vollenhoven RF, Petri M, Wallace DJ, Roth DA, Molta CT, Hammer AE, et al. Cumulative corticosteroid dose over fifty-two weeks in patients with systemic lupus erythematosus: pooled analyses from the phase III belimumab trials. Arthritis Rheumatol 2016;68: 2184–92.