

**PAPER****A 6-month open-label extension study of the safety and efficacy of subcutaneous belimumab in patients with systemic lupus erythematosus**A Doria<sup>1</sup>, D Bass<sup>2</sup>, A Schwarting<sup>3,4</sup>, A Hammer<sup>2</sup>, D Gordon<sup>2,\*</sup>, M Scheinberg<sup>5</sup>, NL Fox<sup>6,\*</sup>, J Groark<sup>2</sup>, W Stohl<sup>7</sup>, C Kleoudis<sup>8</sup> and D Roth<sup>2</sup>

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**Objective:** To evaluate the safety, tolerability and efficacy of subcutaneous (SC) belimumab in patients with systemic lupus erythematosus (SLE) beyond 1 year. **Methods:** This was a 24-week, open-label extension following a 52-week, double-blind, placebo-controlled trial of belimumab SC. Patients who completed the double-blind phase were eligible to enter the open-label phase. All patients received weekly belimumab 200 mg SC plus standard SLE therapy. Outcome measures included safety and efficacy (SLE Response Index (SRI) and SLE Flare Index (SFI) rates), and changes in biomarker and B cell levels. **Results:** Of 677 patients who completed the 52-week, double-blind phase, 662 entered the open-label phase; 206 had previously received placebo and 456 had previously received belimumab. Despite differences in total belimumab exposure (24 weeks in the placebo-to-belimumab group versus 76 weeks in the belimumab group), the proportions of patients experiencing more than one adverse event (AE) or a serious AE in the open-label phase were similar between groups (placebo-to-belimumab: 51.5 and 6.8%; belimumab: 48.2 and 5.5%, respectively). Most AEs were mild/moderate in severity. Efficacy was maintained through the extension phase. An SRI response was achieved by 16.1% of patients in the placebo-to-belimumab group and 76.3% patients in the belimumab group. Furthermore, 1.0% of patients in the placebo-to-belimumab group and 2.6% of patients in the belimumab group experienced a severe SFI flare. **Conclusion:** Belimumab SC was well tolerated and efficacy was maintained during the extension phase of this study. The safety profile of belimumab SC is consistent with that of previous experience with belimumab. **Trial registration:** ClinicalTrials.gov identifier: NCT01484496 *Lupus* (2018) 27, 1489–1498.

**Key words:** Belimumab; B-lymphocyte stimulator; corticosteroids; open-label extension; SLE responder index; subcutaneous; systemic lupus erythematosus

**Introduction**

Belimumab is a human monoclonal antibody that binds to and inhibits the biological activity of B-lymphocyte stimulator,<sup>1</sup> a potent B cell survival factor associated with human systemic lupus

erythematosus (SLE) disease.<sup>2</sup> Intravenous (IV) belimumab 10 mg/kg was the first, and to date only, biological drug to be approved for the treatment of adult patients with active, autoantibody-positive SLE.<sup>3–5</sup> Since its approval, evidence from clinical practice has demonstrated that belimumab is associated with improvements in control of disease activity, reductions in fatigue and improvements in ability to work.<sup>6</sup> Therefore, belimumab is cost-effective both in terms of employment and in decreasing health resource utilization.<sup>6</sup>

Although the approval of belimumab IV was a significant step in improving treatment options for patients with SLE, the IV administration route can

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pose challenges for some patients. Belimumab IV must be administered at a clinic or infusion centre, which is resource-intensive for the healthcare system and time-consuming for patients. Hence, to enhance usability, a new subcutaneous (SC) formulation of belimumab has been developed.<sup>7</sup> Comparison of weekly dosing of belimumab 200 mg SC with belimumab 10 mg/kg IV administered every 4 weeks demonstrated that the dosing regimens result in similar exposure.<sup>8,9</sup> Belimumab SC administration may provide greater convenience to patients versus IV administration due to its less invasive and quicker administration time. Moreover, it can be administered outside of the doctor's clinic by patients or their caregivers. These advantages of SC administration are particularly important for the chronic long-term treatment of SLE.<sup>10–12</sup>

A study of belimumab administered subcutaneously in subjects with SLE (BLISS-SC) (GlaxoSmithKline [GSK] study BEL112341; NCT01484496), a 52-week Phase III, double-blind study, demonstrated the efficacy and safety of belimumab SC delivered via a prefilled syringe in patients with active, autoantibody-positive SLE. Weekly doses of belimumab 200 mg SC plus standard SLE therapy (SoC) significantly improved the SLE Response Index 4 (SRI4) response and reduced the incidence of severe flares compared with placebo. Moreover, belimumab was generally well tolerated and the rates of adverse events (AEs) were similar across belimumab and placebo groups.<sup>7</sup> Here, we present the results of a 6-month extension to BLISS-SC, conducted to evaluate the safety, tolerability and efficacy of belimumab SC in patients with SLE who completed the 52-week parent study.

## Methods

### *Study design*

This was a 24-week multicentre, open-label extension phase of the BLISS-SC study (GSK study BEL112341; NCT01484496), conducted between November 2011 and October 2015 at 177 sites in 30 countries across North America, Central America, South America, Western Europe, Eastern Europe and Asia.<sup>7</sup> Details of the BLISS-SC study design have been reported previously.<sup>7</sup>

### *Patients*

Patient inclusion and exclusion criteria for the BLISS-SC study have been described previously.<sup>7</sup>

In brief, at screening, patients were  $\geq 18$  years of age with a diagnosis of SLE classified according to the American College of Rheumatology criteria,<sup>13</sup> a Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score  $\geq 8$  and were antinuclear antibody and/or anti-double-stranded DNA (dsDNA) positive.<sup>7</sup> Patients with severe lupus kidney disease or severe central nervous system lupus were excluded. Patients who completed the 52-week double-blind phase were eligible to participate in the open-label extension phase.<sup>7</sup> Patients who had previously received placebo in the double-blind phase were switched to belimumab 200 mg SC weekly in the extension phase (placebo-to-belimumab group); patients who had previously received belimumab 200 mg SC continued to receive the same dose (belimumab group) (Figure 1). Patients received the first dose of belimumab approximately 1 week after the last dose in the double-blind phase of the study. All patients received SoC throughout the study.

All patients provided written informed consent prior to enrolment. Ethics committee/institutional review board approval was obtained for all study sites. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki 2008, the International Council for Harmonisation on Good Clinical Practice and the applicable country-specific regulatory requirements.<sup>14</sup>

### *Endpoints and assessments*

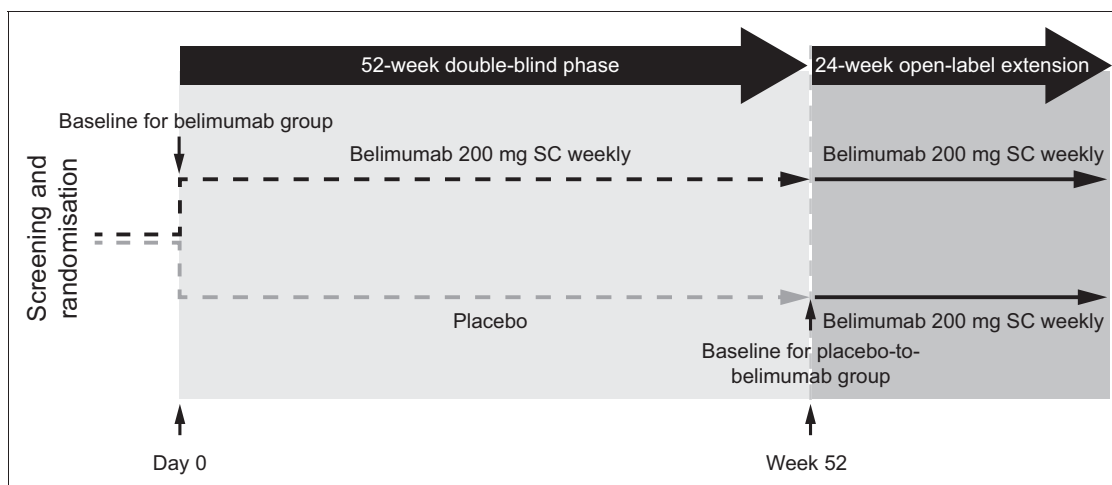
#### *Safety*

The safety of belimumab was evaluated by monitoring AEs, serious AEs (SAEs), AEs of special interest (AESIs; malignancies, post-injection systemic reactions, infections, depression/suicide/self-injury and deaths), clinical laboratory tests (haematology, chemistry and routine urinalysis) and immunogenicity throughout the 24-week extension phase. AEs were coded according to the Medical Dictionary for Regulatory Activities Version 18.

#### *Efficacy*

For all efficacy analyses, baseline was defined as the last assessment prior to the first dose of belimumab; for the belimumab group, this was day 0 of the double-blind phase and for the placebo-to-belimumab group, this was week 52 of the double-blind phase.

Efficacy was evaluated by SRI4 at week 24 and is defined as a  $\geq 4$ -point reduction from baseline in SELENA-SLEDAI score, no worsening (increase



**Figure 1** Study design of BLISS-SC trial and subsequent open-label extension phase. BLISS-SC: A study of belimumab administered subcutaneously in subjects with systemic Lupus Erythematosus; SC: subcutaneous.

of  $<0.30$  points from baseline) in Physician's Global Assessment (PGA), and no new British Isles Lupus Assessment Group (BILAG) A organ domain score or two new BILAG B organ domain scores compared with baseline.<sup>15</sup> Other efficacy assessments included time to first severe SFI flare during the open-label phase, percentage of patients with daily prednisone dose reduced from  $>7.5$  mg/day at baseline to  $\leq 7.5$  mg/day at week 24, percentage of patients with daily prednisone dose increased from  $\leq 7.5$  mg/day at baseline to  $>7.5$  mg/day at week 24, time to first renal flare and time to first renal flare among patients with baseline proteinuria  $>0.5$  g/24 hours.

#### Biomarkers

Biomarker assessments included changes in anti-dsDNA, serum complement levels (C3 and C4) and mean percent change from baseline in B cell subsets (CD20+; CD19+/CD20+/CD27-naïve; CD19+/CD20+/CD69+ activated; CD19+/CD20+/CD27+ memory; CD19+/CD20+/CD138+ plasmacytoid; CD19+/CD20-/CD138+ plasma cells; CD19+/CD38b+/CD27b lymph SLE subset; and CD19+/CD24b+/CD38b+/CD27- transitional).

#### Data analyses

Enrolment in the open-label extension phase was dependent on the number of patients completing the 52-week parent study; therefore, no sample size calculations were performed.

All analyses were conducted in the intent-to-treat population, defined as all randomized patients who received at least one dose of belimumab in the extension phase.

No formal statistical hypothesis testing was performed for the open-label phase.

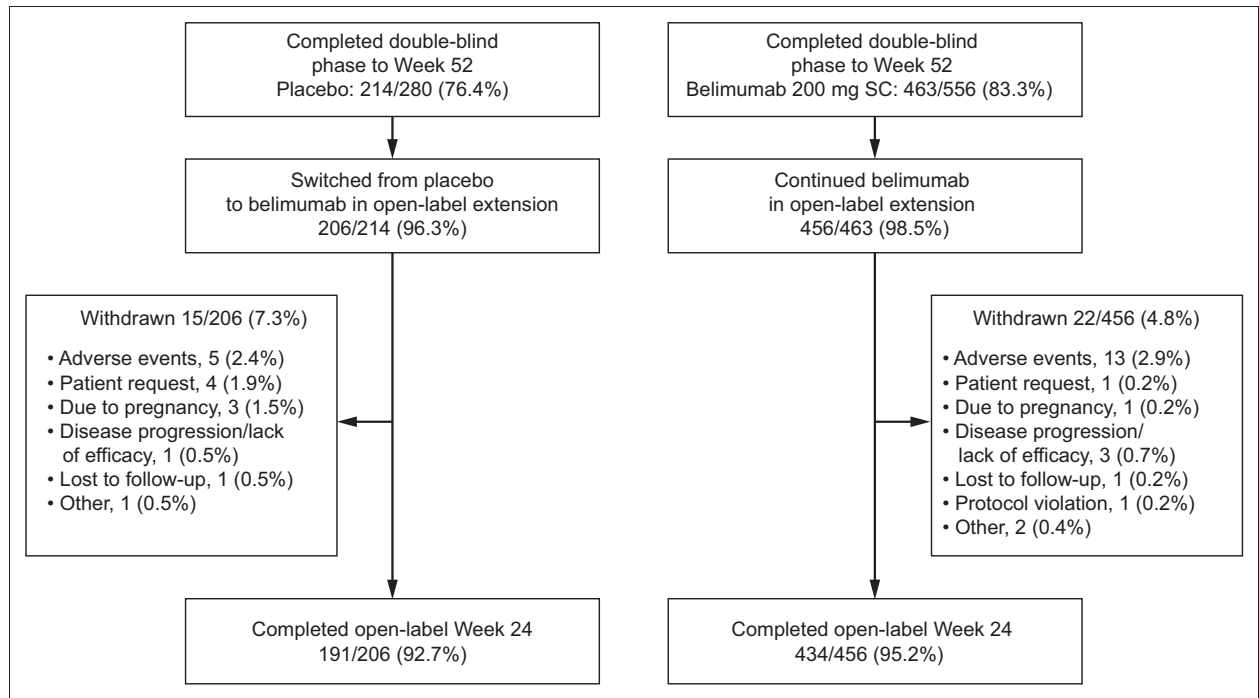
Continuous variables were summarized using mean, median, standard deviation (SD), 25th and 75th percentile, and minimum and maximum values. The analyses were performed using SAS software version 9.3 (SAS Institute Inc., Cary, NC, USA).

## Results

### Patient population

Of 677 patients who completed the 52-week double-blind phase, 662 (97.8%) entered the open-label extension phase. Of these, 206 patients who had received placebo during the double-blind phase were switched to belimumab 200 mg SC and 456 patients who had received belimumab 200 mg SC during the double-blind phase continued to do so in the open-label extension phase (Figure 2). A total of 625 (94.4%) patients completed the open-label extension phase and 37 (5.6%) withdrew. The most common reason for withdrawal was AEs, which were observed at a similar frequency in both treatment groups (placebo-to-belimumab: 2.4%; belimumab: 2.9%).

Baseline (last assessment prior to the first dose of belimumab) demographics were similar between treatment groups (Table 1); the majority of patients were female (94.6%; 626/662), with a mean (SD) age of 38.7 (11.86) years. Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index scores were similar between groups; however, patients



**Figure 2** Patient disposition. SC, subcutaneous.

in the placebo-to-belimumab group had lower BILAG, SELENA-SLEDAI and PGA scores compared with the belimumab group (Table 1). There were 55 (26.7%) patients in the placebo-to-belimumab group who had a baseline SELENA-SLEDAI score < 4 as a result of improvements that occurred between screening prior to the start of the double-blind phase and baseline (week 52 of the double-blind phase). Two (0.4%) patients in the belimumab group had a baseline SELENA-SLEDAI score < 4 due to fluctuations occurring between screening and baseline. Patients with a SELENA-SLEDAI score < 4 at baseline were excluded from the SELENA-SLEDAI analyses.

### Safety

#### Adverse events

Despite the differences in cumulative belimumab exposure (placebo-to-belimumab: 24-week open-label extension only; belimumab: 52-week double-blind phase plus 24-week open-label extension), the proportion of patients experiencing an AE during the 24-week open-label extension was similar between the treatment groups (placebo-to-belimumab: 51.5%; belimumab: 48.2%) (Table 2). The majority of AEs were mild to moderate in severity. Infections and infestations were the most frequent AEs by system organ class (placebo-to-belimumab: 29.6%; belimumab: 28.3%) (Table 2). SAEs

occurred in 6.8% of patients in the placebo-to-belimumab group and 5.5% of patients in the belimumab group. The incidence of serious infections and infestations was 3.4% in the placebo-to-belimumab group compared with 2.2% in the belimumab group. AEs leading to discontinuation of belimumab occurred in 5 (2.4%) patients in the placebo-to-belimumab group and 12 (2.6%) patients in the belimumab group.

Overall, the incidence of AESIs was low. The incidence of post-injection systemic reactions was 4.4% (9/206) in the placebo-to-belimumab group and 2.6% (12/456) in the belimumab group. The incidence of local injection-site reactions was 1.5% (3/206) in the placebo-to-belimumab group and 0.2% (1/456) in the belimumab group; none were serious or resulted in study discontinuation. Four (1.9%) patients in the placebo-to-belimumab group and 8 (1.8%) patients in the belimumab group experienced depression. One (0.2%) patient in the belimumab group had a suicide attempt that did not result in death (Table 2).

Two deaths occurred in the open-label phase. Metabolic acidosis occurred in a 40-year-old male in the placebo-to-belimumab group who developed grade 4 SAEs of deep vein thrombosis, antiphospholipid syndrome, acute kidney injury and metabolic acidosis 31 days after receiving the first dose of belimumab 200 mg SC. Grade 4 acute

**Table 1** Baseline patient demographics and characteristics (intent-to-treat population)

Characteristic	Placebo-to-belimumab 200 mg SC n = 206	Belimumab 200 mg SC n = 456
<b>Female, n (%)</b>	196 (95.1)	430 (94.3)
<b>Age (years), mean (SD)</b>	39.4 (12.04)	38.3 (11.77)
<b>Weight (kg), mean (SD)</b>	70.0 (20.27)	68.4 (17.67)
<b>Enrolment by region, n (%)</b>		
USA	56 (27.2)	109 (23.9)
Americas excluding USA	39 (18.9)	101 (22.1)
Western Europe	14 (6.8)	40 (8.8)
Eastern Europe	48 (23.3)	112 (24.6)
Asia	49 (23.8)	94 (20.6)
<b>Ethnicity, n (%)</b>		
Hispanic or Latino	59 (28.6)	135 (29.6)
Not Hispanic or Latino	147 (71.4)	321 (70.4)
<b>Disease duration (years), median (range)</b>	4.8 (1, 33)	4.5 (0, 35)
<b>SELENA-SLEDAI, mean (SD)<sup>a</sup></b>	5.8 (3.90)	10.4 (3.16)
<b>SELENA-SLEDAI organ involvement, n (%)</b>		
Mucocutaneous	108 (52.4)	397 (87.1)
Musculoskeletal	54 (26.2)	367 (80.5)
Immunological	151 (73.3)	349 (76.5)
Renal	24 (11.7)	42 (9.2)
Haematological	10 (4.9)	30 (6.6)
Vascular	7 (3.4)	39 (8.6)
Cardiovascular and respiratory	4 (1.9)	20 (4.4)
Constitutional	0	6 (1.3)
CNS	1 (0.5)	7 (1.5)
<b>BILAG organ domain involvement<sup>b</sup>, n (%)</b>		
≥ 1A or 2B	42 (20.4)	314 (68.9)
≥ 1A	5 (2.4)	69 (15.1)
≥ 1B	123 (59.7)	405 (88.8)
No A or B	79 (38.3)	26 (5.7)
<b>PGA, mean (SD)</b>	0.8 (0.55)	1.6 (0.41) <sup>c</sup>
<b>Anti-dsDNA ≥ 30 IU/mL, n (%)</b>	126 (61.8)	333 (73.0)
<b>Low C3 (&lt; 90 mg/dL), n (%)</b>	91 (44.6)	201 (44.1)
<b>Low C4 (&lt; 10 mg/dL), n (%)</b>	45 (22.1)	119 (26.1)
<b>FACIT-Fatigue, mean (SD)</b>	36.5 (11.45)	32.2 (12.01) <sup>d</sup>
<b>Medications, n (%)</b>		
Corticosteroid only	23 (11.2)	44 (9.6)
Antimalarial only	11 (5.3)	31 (6.8)
Immunosuppressant only	4 (1.9)	9 (2.0)
Corticosteroid and antimalarial only	72 (35.0)	172 (37.7)
Corticosteroid and immunosuppressant only	38 (18.4)	70 (15.4)
Immunosuppressant and antimalarial only	14 (6.8)	12 (2.6)
Corticosteroid, immunosuppressant and antimalarial	41 (19.9)	112 (24.6)

Baseline was defined as the last assessment prior to the first dose of belimumab; for the belimumab group this was day 0 of the double-blind phase and for the placebo-to-belimumab group this was week 52 of the double-blind phase.

<sup>a</sup>Among all patients; however, 55 patients in the placebo-to-belimumab group and 2 patients in the belimumab group had a baseline SELENA-SLEDAI score < 4.

<sup>b</sup>Patients may be included in more than one category.

<sup>c</sup>n = 455.

<sup>d</sup>n = 454.

BILAG: British Isles Lupus Assessment Group; C3: complement 3; C4: complement 4; CNS: central nervous system; dsDNA: double-stranded DNA; FACIT: Functional Assessment of Chronic Illness Therapy; PGA: Physician's Global Assessment; SC: subcutaneous; SD: standard deviation; SELENA-SLEDAI: Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index; SLE: systemic lupus erythematosus.

respiratory failure occurred in a 37-year-old female in the belimumab group, who developed pneumonia 393 days after receiving the first dose of belimumab 200 mg SC.

#### Clinical laboratory evaluations

The percentage of patients with worsening (≥ 2 grade) of clinical laboratory parameters (haematology, liver function, electrolyte parameters, all other



**Table 2** Summary of adverse events

	Placebo-to-belimumab 200 mg SC n = 206	Belimumab 200 mg SC n = 456
<b>Any event, n (%)</b>	106 (51.5)	220 (48.2)
<b>AEs by system organ class<sup>a</sup>, n (%)</b>		
Infections and infestations	61 (29.6)	129 (28.3)
Gastrointestinal disorders	14 (6.8)	41 (9.0)
Musculoskeletal and connective tissue disorders	19 (9.2)	36 (7.9)
Nervous system disorders	20 (9.7)	26 (5.7)
Skin and subcutaneous tissue disorders	20 (9.7)	20 (4.4)
General disorders and administration site conditions	14 (6.8)	25 (5.5)
<b>AEs by preferred term<sup>b</sup>, n (%)</b>		
Viral upper respiratory tract infection	9 (4.4)	17 (3.7)
Arthralgia	7 (3.4)	11 (2.4)
Urinary tract infection bacterial	2 (1.0)	15 (3.3)
Nasopharyngitis	9 (4.4)	7 (1.5)
<b>SAEs<sup>c</sup>, n (%)</b>	14 (6.8)	25 (5.5)
Infections and infestations	7 (3.4)	10 (2.2)
<b>AEs resulting in study discontinuation, n (%)</b>	5 (2.4)	12 (2.6)
<b>AEs of special interest, n (%)</b>		
Malignancies	0	0
Post-injection systemic reactions <sup>d</sup>	9 (4.4)	12 (2.6)
Serious	0	0
Serious delayed non-acute hypersensitivity reactions <sup>d</sup>	0	0
All infections of special interest	7 (3.4)	10 (2.2)
Serious	3 (1.5)	2 (0.4)
Opportunistic infections <sup>d</sup>	2 (1.0)	1 (0.2)
Serious	2 (1.0)	1 (0.2)
<i>Herpes zoster</i>	6 (2.9)	6 (1.3)
Serious	2 (1.0)	0
Sepsis	0	2 (0.4)
Serious	0	1 (0.2)
Depression	4 (1.9)	8 (1.8)
Serious	0	1 (0.2)
Serious suicidal ideation/self injury <sup>d</sup>	0	1 (0.2)
Suicidal behaviour <sup>d</sup>	0	1 (0.2)
<b>Deaths, n (%)</b>	1 (0.5)	1 (0.2)

<sup>a</sup>AEs that occurred in  $\geq 5\%$  of patients in either treatment group are listed.

<sup>b</sup>AEs that occurred in  $\geq 3\%$  of patients in either treatment group are listed.

<sup>c</sup>SAEs that occurred in  $> 2\%$  of patients in either treatment group are listed.

<sup>d</sup>Per GlaxoSmithKline adjudication.

AEs: adverse events; SAEs: serious AEs; SC: subcutaneous.

chemistries and urinalysis) from baseline was low ( $< 4\%$  of all patients) (Supplementary Table 1). Overall, 0.5% of patients in the placebo-to-belimumab group and 0.4% of patients in the belimumab group had a grade 0 to grade 2 change in immunoglobulin G.

#### Immunogenicity

Three (0.5%) patients (2 [1.2%] in the placebo-to-belimumab group and 1 [0.3%] in the belimumab group) developed circulating anti-belimumab antibodies during the open-label phase, which subsequently resolved in each patient. None of these patients experienced an SAE; one reported a post-injection systemic reaction (rash), which was

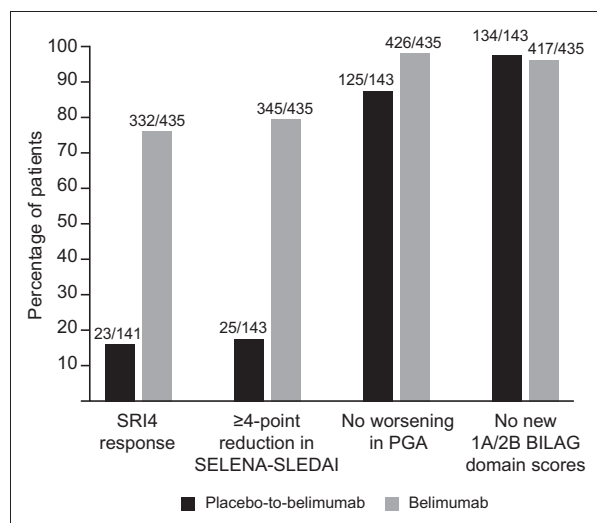
mild in severity and was not a hypersensitivity reaction.

#### Efficacy

##### SRI response

At week 24, 16.1% (23/143) of patients in the placebo-to-belimumab group and 76.3% (332/435) of patients in the belimumab group achieved an SRI4 response (Figure 3).

A  $\geq 4$ -point improvement in SELENA-SLEDAI, no worsening in PGA and no new BILAG 1A/2B score were reported for 17.5% (25/143), 87.4% (125/143), and 93.7% (134/143) of the placebo-to-belimumab group, respectively, and 79.3% (345/



**Figure 3** Systemic lupus erythematosus Responder Index response at week 24.

BILAG: British Isles Lupus Assessment Group; PGA: Physician's Global Assessment; SELENA-SLEDAI: Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index; SRI: Systemic lupus erythematosus Responder Index.

435), 97.9% (426/435) and 95.9% (417/435) of the belimumab group, respectively.

#### SFI flare

During the open-label phase, 1.0% (2/206) of patients in the placebo-to-belimumab group and 2.6% (12/456) of patients in the belimumab group had a severe flare. Among these patients, median (range) time to first severe flare was 168.5 (167, 170) days in the placebo-to-belimumab group and 169.0 (117, 194) days in the belimumab group. In total, 18.4% (38/206) of patients in the placebo-to-belimumab group and 12.7% (58/456) in the belimumab group had any (mild, moderate or severe) flare during the open-label extension.

#### Renal flares

Renal flares (mild, moderate or severe) occurred in 1.5% (3/206) of patients in the placebo-to-belimumab group and 3.5% (16/456) of patients in the belimumab group. Among patients with baseline proteinuria > 0.5 g/24 hours, fewer patients in the placebo-to-belimumab group (6.3%, 2/32) had a renal flare compared with the belimumab group (9.3%, 7/75).

#### Prednisone use

Among patients receiving a baseline prednisone dose > 7.5 mg/day, 9.8% (10/102) in the placebo-to-belimumab group and 24.4% (67/275) in the

belimumab group had a dose reduction to ≤ 7.5 mg/day by week 24. In patients with baseline prednisone dose ≤ 7.5 mg/day, 1.9% (2/104) of the placebo-to-belimumab group and 5.0% (9/181) of the belimumab group had a dose increase to > 7.5 mg/day.

#### Biomarkers

Among patients with anti-dsDNA antibodies at baseline, the median (25th, 75th percentile) reductions at week 24 were -35.6% (-51.9%, -9.2%;  $n=121$ ) in the placebo-to-belimumab group and -62.8% (-77.9%, -39.0%;  $n=326$ ) in the belimumab group. Of the patients who were anti-dsDNA antibody-positive at baseline, 13.2% (16/121) in the placebo-to-belimumab group and 21.5% (70/326) in the belimumab group were anti-dsDNA antibody-negative at week 24 (Table 3).

Among patients with low C3 levels at baseline (< 90 mg/dL), the mean (SD) percent changes in C3 from baseline to week 24 were 16.7% (23.46;  $n=88$ ) and 29.1% (38.11;  $n=198$ ) for the placebo-to-belimumab and belimumab groups, respectively. In patients with low C4 levels at baseline (< 10 mg/dL), the mean (SD) percent changes in C4 levels were 50.6% (82.69;  $n=43$ ) and 77.6% (83.44;  $n=117$ ) for the placebo-to-belimumab and belimumab groups, respectively (Table 3).

From baseline to week 24, there were greater reductions in levels of CD19+, CD20+, naïve (CD19+/CD20+/CD27-) and activated (CD19+/CD20+/CD69+) B cells among patients in the belimumab group compared with the placebo-to-belimumab group (Table 3).

#### Discussion

This 6-month extension of the BLISS-SC study examined the safety, tolerability and efficacy of belimumab SC in patients with SLE and demonstrates comparable safety and efficacy to that observed in the 52-week, double-blind phase of the study.<sup>7</sup>

In this open-label phase, belimumab was well tolerated over 24 weeks of treatment, with an overall incidence rate of AEs similar to that observed in the 52-week double-blind phase.<sup>7</sup> Most AEs were of mild or moderate intensity. The overall rate of treatment discontinuation due to AEs was lower in the open-label phase compared with that reported in the 52-week double-blind phase. The rates of AESIs were low and there were no discontinuations due to infections of special interest. The

**Table 3** Changes in biomarker measures from baseline at week 24

Biomarker	Placebo-to-belimumab 200 mg SC (n = 206)	Belimumab 200 mg SC (n = 456)
<b>Serological measures</b>		
Anti-dsDNA antibody level		
Positive <sup>a</sup> at baseline, n	121	326
Shift from positive <sup>a</sup> to negative, n (%)	16 (13.2)	70 (21.5)
Negative at baseline, n	77	122
Shift from negative to positive <sup>a</sup> , n (%)	2 (2.6)	4 (3.3)
C3		
Low <sup>b</sup> at baseline, n	88	198
Low <sup>b</sup> to normal/high <sup>c</sup> , n (%)	31 (35.2)	95 (48.0)
Normal/high <sup>c</sup> at baseline, n	110	250
Normal/high <sup>c</sup> to low <sup>b</sup> , n (%)	12 (10.9)	19 (7.6)
C4		
Low <sup>d</sup> at baseline, n	43	117
Low <sup>d</sup> to normal/high <sup>c</sup> n (%)	23 (53.5)	64 (54.7)
Normal/high <sup>c</sup> at baseline, n	155	331
Normal/high <sup>c</sup> to low <sup>d</sup> n (%)	4 (2.6)	13 (3.9)
<b>B cell subsets<sup>f</sup></b>		
CD19+, n	194	443
Median % change (25th and 75th percentile)	-25.3 (-57.5, 18.0)	-64.6 (-79.4, -40.3)
CD20+, n	192	421
Median % change (25th and 75th percentile)	-26.4 (-57.9, 22.6)	-64.5 (-79.8, -38.9)
Naïve CD19+CD20+CD27-, n	192	421
Median % change (25th and 75th percentile)	-47.4 (-69.2, -11.0)	-76.0 (-86.6, -58.4)
Activated CD19+CD20+CD69+, n	178	406
Median % change (25th and 75th percentile)	-52.3 (-87.5, 10.3)	-73.3 (-93.7, -26.8)
Memory CD19+CD20+CD27+, n	192	421
Median % change (25th and 75th percentile)	82.0 (33.3, 197.2)	0.0 (-42.3, 57.1)
Plasmacytoid CD19+CD20+CD138+, n	166	393
Median % change (25th and 75th percentile)	-22.2 (-79.9, 88.5)	-67.5 (-93.4, 8.3)
Plasma CD19+CD20-CD138+, n	184	412
Median % change (25th and 75th percentile)	-54.3 (-86.1, 71.5)	-74.3 (-92.7, -17.7)
SLE subset CD19+CD38b+CD27b+Lymph, n	192	422
Median % change (25th and 75th percentile)	-43.8 (-68.4, 9.5)	-64.3 (-83.4, -24.0)
Transitional CD19+CD24b+CD38b+CD27-, n	186	412
Median % change (25th and 75th percentile)	-65.1 (-84.4, 0.5)	-63.8 (-84.1, -0.8)

<sup>a</sup> ≥ 30 IU/mL.

<sup>b</sup> < 90 mg/dL.

<sup>c</sup> ≥ 90 mg/dL.

<sup>d</sup> < 10 mg/dL.

<sup>e</sup> ≥ 10 mg/dL.

<sup>f</sup>Patients with a baseline score of 0 were excluded from the analysis.

Anti-dsDNA: antidouble-stranded DNA; C3: complement 3; C4: complement 4; SC: subcutaneous; SLE: systemic lupus erythematosus.

safety profile of belimumab SC in this study is in line with that demonstrated in the Phase III double-blind and open-label extension studies of belimumab IV,<sup>16-18</sup> and in clinical practice.<sup>19,20</sup>

The efficacy of belimumab was maintained throughout the open-label phase. An SRI response was achieved by 16.1% of patients in the placebo-to-belimumab group who received belimumab for 24 weeks, and 76.3% patients in the belimumab group who received belimumab for a total of 76 weeks. At the end of the double-blind phase (52 weeks), 61.4% of the belimumab group had an SRI response;<sup>7</sup> therefore, during the open-label phase, efficacy was

maintained or improved with ongoing exposure to belimumab. These results suggest that 24 weeks of belimumab may not be sufficient for a complete response. However, the higher SRI response rate observed in the belimumab group compared with the placebo-to-belimumab group could also be due to the lower baseline SELENA-SLEDAI in the placebo-to-belimumab group compared with the belimumab group, which made it more difficult to demonstrate improvement. Furthermore, since the SRI response requires a four-point reduction in SELENA-SLEDAI and 55 patients in the placebo-to-belimumab group had a baseline



SELENA-SLEDAI score of  $<4$  at the start of the open-label extension, they were excluded from this analysis. The rate of severe flares was low across the entire study population. Among patients receiving a baseline prednisone dose  $>7.5$  mg/day, 9.8% in the placebo-to-belimumab group and 24.4% in the belimumab group had a dose reduction to  $\leq 7.5$  mg/day by week 24; this is concordant with Phase III double-blind studies of belimumab IV.<sup>16,18</sup>

There are several limitations to the interpretation of these data. First, there was no placebo control arm during the open-label extension; therefore, results cannot be definitively attributed to belimumab. Moreover, the baseline clinical characteristics for the placebo-to-belimumab group were different from those for the belimumab group, due to the difference in timing of the baselines and differences in the inclusion criteria of the two phases of the study. The duration of exposure to belimumab differed between the two treatment groups; therefore, no comparisons are made between the groups. Patients who were randomized to placebo had lower disease activity at baseline for the open-label phase compared with baseline in the double-blind phase, reflecting improvements in disease activity during the double-blind phase.<sup>7</sup> Additionally, patients were required to have a SELENA-SLEDAI score  $\geq 8$  to be eligible to enter into the 52-week, double-blind phase, whereas there was no such criterion for inclusion in the open-label phase. As such, 55 patients in the placebo-to-belimumab group had a baseline SELENA-SLEDAI score of  $\leq 4$  and were excluded from the SRI analyses; in the belimumab group there were four patients who were excluded from the analyses due to having a baseline SELENA-SLEDAI score of  $\leq 4$ . There may have been some selection bias as patients who completed the double-blind phase and were therefore eligible to enter the extension phase were those who responded to or tolerated belimumab or placebo in the double-blind phase. Patients who maintained disease control or improved while receiving placebo plus SoC in the double-blind phase may represent patients with stable, less active disease. Furthermore, the treatment groups received belimumab for different durations; therefore, statistical comparisons between the two groups cannot be made.

In summary, belimumab 200 mg SC as add-on therapy to SoC was well tolerated in patients with SLE during this 24-week extension phase of the BLISS-SC study. The safety profile was in line with that observed during the double-blind phase, with no increase in AEs and SAEs, and no new safety signals. Moreover, the efficacy of belimumab was maintained across the extension phase.

Together with the ease of use, financial and time-saving benefits of the SC route of administration,<sup>7,10,12</sup> the results of this study suggest that belimumab SC could provide a desirable additional treatment option for patients with SLE.

### Key messages

- The safety and tolerability of up to 76 weeks' treatment with subcutaneous belimumab is acceptable.
- The efficacy of subcutaneous belimumab was maintained during this open-label extension phase.
- Subcutaneous belimumab will provide an additional treatment option for patients with systemic lupus erythematosus.

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### Availability of study materials

The study protocol and clinical study report are freely available from <https://gsk-clinicalstudyregister.com/>

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