

PAPER**Long-term organ damage accrual and safety in patients with SLE treated with belimumab plus standard of care**IN Bruce^{1,2}, M Urowitz³, R van Vollenhoven⁴, C Aranow⁵, J Fettiplace⁶, M Oldham⁷, B Wilson^{8,*}, C Molta^{9,*}, D Roth⁹ and D Gordon⁹

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Objective: To examine long-term organ damage and safety following treatment with belimumab plus standard of care (SoC) in patients with systemic lupus erythematosus (SLE). **Methods:** Pooled data were examined from two ongoing open-label studies that enrolled patients who completed BLISS-52 or BLISS-76. Patients received belimumab every four weeks plus SoC. SLICC Damage Index (SDI) values were assessed every 48 weeks (study years) following belimumab initiation (baseline). The primary endpoint was change in SDI from baseline at study years 5–6. Incidences of adverse events (AEs) were reported for the entire study period. **Results:** The modified intent-to-treat (MITT) population comprised 998 patients. At baseline, 940 (94.2%) were female, mean (SD) age was 38.7 (11.49) years, and disease duration was 6.7 (6.24) years. The mean (SD) SELENA-SLEDAI and SDI scores were 8.2 (4.18) and 0.7 (1.19), respectively; 411 (41.2%) patients had organ damage (SDI = 1: 235 (23.5%); SDI ≥ 2: 176 (17.6%)) prior to belimumab. A total of 427 (42.8%) patients withdrew overall; the most common reasons were patient request (16.8%) and AEs (8.5%).

The mean (SD) change in SDI was +0.2 (0.48) at study years 5–6 ($n=403$); 343 (85.1%) patients had no change from baseline in SDI score (SDI +1: 46 (11.4%), SDI +2: 13 (3.2%), SDI +3: 1 (0.2%)). Of patients without organ damage at baseline, 211/241 (87.6%) had no change in SDI and the mean change (SD) in SDI was +0.2 (0.44). Of patients with organ damage at baseline, 132/162 (81.5%) had no change in SDI and the mean (SD) change in SDI was +0.2 (0.53). The probability of not having a worsening in SDI score was 0.88 (95% CI: 0.85, 0.91) and 0.75 (0.67, 0.81) in those without and with baseline damage, respectively (post hoc analysis).

Drug-related AEs were reported for 433 (43.4%) patients; infections/infestations (282, 28.3%) and gastrointestinal disorders (139, 13.9%) were the most common. **Conclusion:** Patients with SLE treated with long-term belimumab plus SoC had a low incidence of organ damage accrual and no unexpected AEs. High-risk patients with pre-existing organ damage also had low accrual, suggesting a favorable effect on future damage development. *Lupus* (2016) 25, 699–709.

Key words: Systemic lupus erythematosus; safety; organ damage

Introduction

Systemic lupus erythematosus (SLE) is a chronic relapsing and remitting condition in which long-term damage may accrue over time as a consequence of both active disease and medication toxicities.^{1,2} The Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) Damage Index (SDI) is

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a validated instrument that has been used in observational cohorts and clinical studies to quantify organ damage. Organ damage, measured by the SDI, is associated with increased morbidity and mortality.^{3,4} SDI items represent irreversible damage occurring after the diagnosis of SLE,⁵ and items present for at least six months become permanent scores, such that the SDI score cannot decrease.⁵

Longitudinal studies of SLE cohorts have shown that mean SDI scores increase over time and that the majority of patients with SLE accrue organ damage.⁶ Factors contributing to irreversible damage have been examined in prospective single-clinic cohort studies and multicenter inception cohorts that allow comparison within studies. Factors associated with an increased risk of organ damage include older age at SLE onset, Hispanic and African ancestry race/ethnicity, existing organ damage, chronic inflammation, hypertension, and chronic steroid exposure.⁵⁻⁹ Patients with damage have consistently been shown to be at risk of accruing additional damage, both in inception and prevalent cohorts.^{5,10-12}

There is evidence that the use of antimalarials may potentially have a “protective” role against damage development. Use of antimalarials in patients with SLE has been associated with reduced disease flares, steroid-sparing effects, and favorable effects on a number of metabolic risk factors, with subsequent “protection” against accruing damage.^{5,13}

Belimumab is a monoclonal antibody targeting B lymphocyte stimulator with proven efficacy in the treatment of SLE when added to standard of care (SoC) therapy.^{14,15} Organ damage and long-term safety of belimumab are currently being examined in two open-label continuation studies that enrolled patients who completed Belimumab in Subjects With Systemic Lupus Erythematosus (BLISS)-52¹⁵ or BLISS-76.¹⁴ We report an analysis of pooled data from these studies to examine long-term safety, with a key focus on damage accrual across five to six study years.

Methods

Study design

This study (201223) pooled data from two ongoing open-label, long-term, continuation studies, BEL112233 (NCT00724867) and BEL112234 (NCT00712933), that enrolled patients who completed the parent studies BLISS-52 (BEL110752,

NCT00424476)¹⁵ or BLISS-76 (BEL110751, NCT00410384)¹⁴ (Figure 1). BLISS-52 and BLISS-76 patients were randomized to belimumab 1 mg/kg, belimumab 10 mg/kg, or placebo plus SoC for 52 or 76 weeks.^{14,15} Patients who completed the parent studies were invited to participate in a long-term continuation study. Patients who received belimumab 10 mg/kg or placebo in the parent studies were administered belimumab 10 mg/kg in the continuation studies. Approximately one-third of patients received belimumab 1 mg/kg in a parent study and initially received that dose in the continuation studies. Study protocols were amended in March 2011 (BEL112233) and July 2011 (BEL112234), and 1 mg/kg patients were switched to 10 mg/kg. Both belimumab dosage groups were combined for the present analyses.

Baseline data were recorded prior to the first dose of belimumab (i.e. first belimumab dose in the parent study or first dose in the continuation study for those who previously received placebo). Visit intervals were defined using actual visit dates based on the 52-week SDI assessment in BLISS-52/76 and the 48-week protocol years in BEL112233/BEL112234. As the parent studies differed in length, SDI assessments and adverse event (AE) reporting were aligned by yearly intervals. The last study visit date was defined as the date of study exit (e.g. exit visit, death, withdrawal, last contact). If the patient was ongoing, and had not completed a study exit visit, the last study visit was defined as the data cutoff date (February 14, 2014). One patient had a last contact date recorded preceding the last infusion date; therefore, the last study visit was set as the final infusion date. Assessments following the last study visit were considered as follow-up and were not included.

All studies were performed in accordance with the Declaration of Helsinki. All sites obtained ethics committee/institutional review board approval and written informed consent was obtained from all patients prior to enrollment.

Patient populations

The analysis was performed on the modified intent-to-treat (MITT) population, defined as all patients from BLISS-52 or BLISS-76 who were enrolled in BEL112233 or BEL112234 and received at least one dose of belimumab (Figure 1). As the SDI study year 5–6 analyses included 30 patients whose SDI assessment was completed prior to five full calendar years, a five-year completer subpopulation was analyzed that included all patients who completed an SDI assessment after at least five full

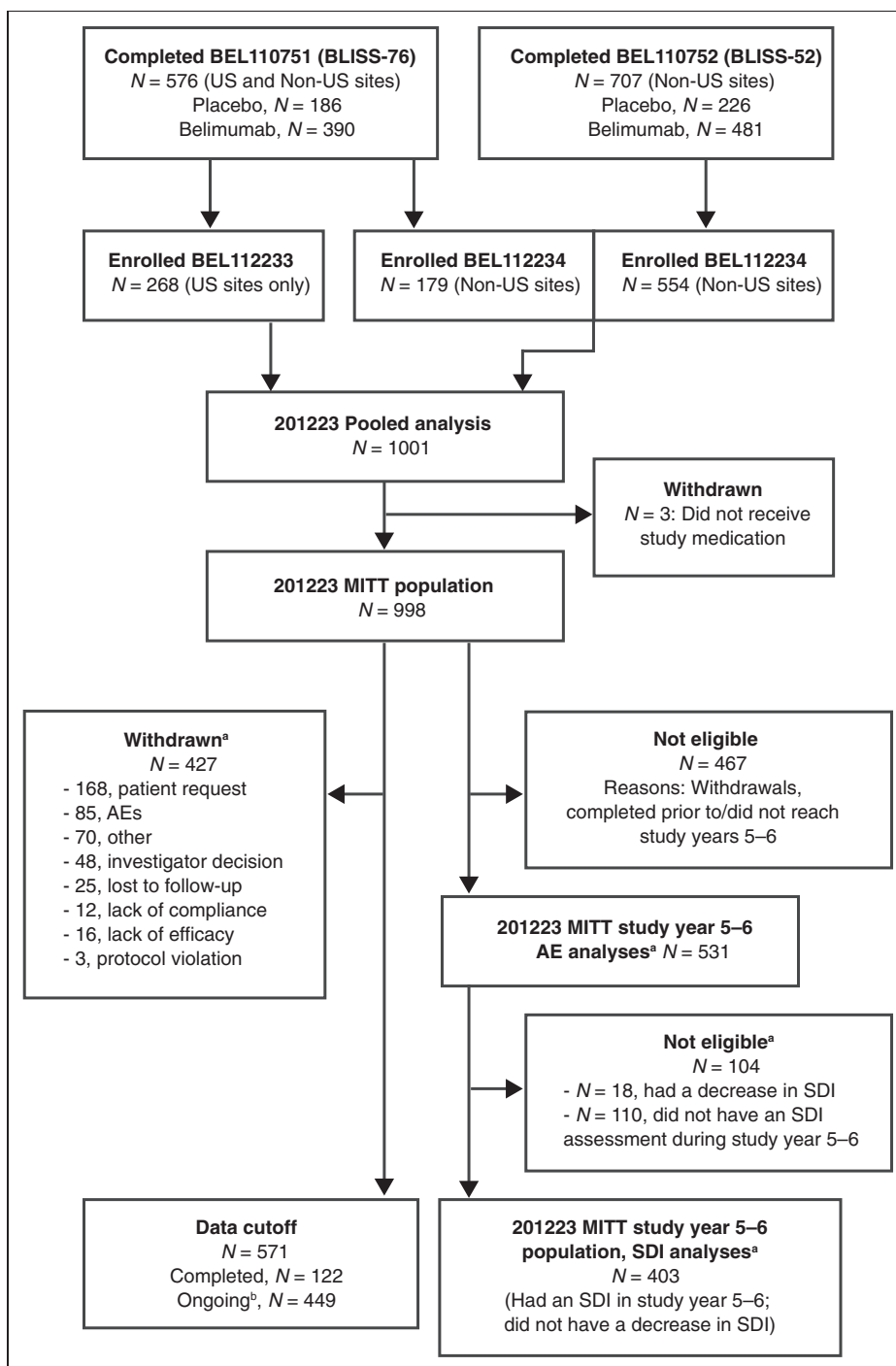


Figure 1 Summary of patient enrollment in the study.

^aPatient numbers at data cutoff. ^bIncludes 11 individuals who had an exit visit but whose completion status was unknown at data cutoff. Ten of these participants were subsequently recorded as completing the study; one withdrew as a result of investigator decision.

AE: adverse event; MITT: modified intent-to-treat; SDI: Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) Damage Index.

calendar years (i.e. after day 1825) of belimumab exposure. A serologically active subpopulation defined as anti-double-stranded DNA (anti-dsDNA)-positive (≥ 30 U/ml) and with low complement (C) 3 or C4 at baseline was also examined.

Study endpoints

Organ damage was assessed using the SDI.^{3,4} The primary endpoint was change in SDI from baseline at study years 5–6; the primary endpoint and change in SDI from baseline by study year were summarized for the MITT population and repeated for the five-year completer and serologically active subpopulations. Secondary endpoints (MITT) included SDI subgroup analyses (baseline SDI 0 or ≥ 1 , baseline Safety of Estrogen in Lupus National Assessment-Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) ≤ 9 or ≥ 10), and time to first SDI worsening.

AEs from the parent and continuation studies were pooled and summarized by study year (Medical Dictionary for Regulatory Activities version 16.1). AEs of special interest included malignant neoplasms, infusion/anaphylaxis/hypersensitivity reactions, infections of special interest (including opportunistic infections, herpes zoster, and sepsis) and depression, suicide/self-injury and deaths.

Statistical analyses

Summary statistics were calculated for continuous variables. Categorical variables were summarized using frequency counts and percentages.

Records for 35 patients (MITT) reported at least one decrease in SDI. As decreases in SDI score are not permitted by definition, these patients were excluded from all SDI analyses.

To eliminate bias in excluding these patients, a post hoc sensitivity analysis (worst observation carried forward, WOCF) was performed in which the highest SDI score for excluded patients was carried forward to subsequent assessments.

Time to first SDI worsening was examined using Kaplan–Meier estimates. In a change from the pre-planned analysis, patients who withdrew/completed prior to their first worsening were censored at their final SDI assessment prior to study exit/data cutoff, instead of last study visit date. Patients who withdrew prior to having a post-baseline SDI assessment were censored at day 0 (treatment start date). Two patients who did not have a baseline SDI score were excluded.

Data were quality checked prior to database release. Because of the ongoing nature of the continuation studies, some data queries were

unresolved at the time of analysis; however, we do not believe that these affect the interpretation of the results.

Results

Study populations

Of 998 patients (MITT, Figure 1, Table 1), 940 (94.2%) were women and the mean (standard deviation (SD)) age at parent study entry was 38.7 (11.49) years. Median (interquartile range, IQR) total belimumab exposure was 1763 (1001–2149) days, with approximately one-third of patients on the 1 mg/kg dose initially. The mean (SD) baseline SELENA-SLEDAI was 8.2 (4.18). The mean (SD) baseline SDI was 0.7 (1.19), and approximately 40% of patients had at least one item of damage (SDI ≥ 1). The mean (SD) SELENA-SLEDAI and the proportions of patients with SELENA-SLEDAI ≥ 10 were slightly higher for the five-year completer subpopulation and the serologically active subpopulation compared with the MITT population (Table 1).

The median (IQR) time to withdrawal from the study was 939 (617–1433) days; 427 (42.8%) patients withdrew (Figure 1, Table 2). Of those who withdrew, patient request was the most common reason (168; 16.8%). A post hoc review of the data indicated that where provided, the two requests most often cited were a desire to conceive and logistical reasons (data not shown). Other common reasons for withdrawal were AEs (85; 8.5%), other (70; 7.0%), and investigator decision (48; 4.8%). The post hoc sensitivity (MITT) analysis showed that the majority of patients (271/307 (88.3%)) who withdrew and had an SDI assessment on the day of withdrawal had no change from baseline in SDI.

Change in SDI

The mean (SD) change in SDI from baseline at study years 5–6 (MITT study year 5–6 population, $n = 403$) was 0.2 (0.48) (Figure 2(a)); 343 (85.1%) had no change in SDI score, 46 (11.4%) had an SDI increase of 1, 13 (3.2%) had an increase of 2, and one (0.2%) had an SDI increase of 3 (Table 3). The majority of patients in the post hoc WOCF analysis (83.1%, study years 5–6, $n = 421$) experienced no change in SDI and the change in SDI from baseline was similar to the MITT study year 5–6 population.

In patients without organ damage at baseline, the mean (SD) SDI change from baseline at study

Table 1 Baseline patient characteristics

Characteristic	MITT (<i>N</i> = 998)	Five-year completers (<i>N</i> = 392)	Serologically active ^a (<i>N</i> = 493)
Female, <i>n</i> (%)	940 (94.2)	365 (93.1)	469 (95.1)
Age, mean (SD)	38.7 (11.49)	39.6 (10.50)	35.4 (10.54)
Weight, mean kg (SD)	67.1 (17.53)	67.3 (17.95)	63.4 (14.58)
BMI, mean (SD)	25.7 (5.97)	25.9 (6.27)	24.3 (5.07)
SLE disease duration (years), mean (SD)	6.7 (6.24)	6.3 (6.15)	6.8 (6.27)
SELENA-SLEDAI, mean (SD)	8.2 (4.18)	9.2 (3.75)	9.4 (3.94)
SELENA-SLEDAI, <i>n</i> (%)			
≤ 9	634 (63.5)	217 (55.4)	257 (52.1)
≥ 10	364 (36.5)	175 (44.6)	236 (47.9)
PGA, mean (SD)	1.2 (0.60)	1.4 (0.48)	1.2 (0.61)
SDI category, <i>n</i> (%)			
0	585 (58.6)	229 (58.4)	310 (62.9)
1	235 (23.5)	94 (24.0)	114 (23.1)
≥ 2	176 (17.6)	69 (17.6)	67 (13.6)
<i>n</i>	996	392	493
Missing	2 (0.2)	0	2 (0.4)
SDI score, mean (SD) ^b	0.7 (1.19)	0.7 (1.13)	0.6 (1.01)
SLE flare index, <i>n</i> (%)			
At least one flare	186 (18.6)	86 (21.9)	93 (18.9)
At least one severe flare	8 (0.8)	1 (0.3)	6 (1.2)
BILAG organ domain, <i>n</i> (%)			
At least 1A or 2B	462 (46.3)	235 (59.9)	215 (43.6)
At least 1A	128 (12.8)	62 (15.8)	58 (11.8)
At least 1B	738 (73.9)	331 (84.4)	362 (73.4)
No A or B	224 (22.4)	45 (11.5)	108 (21.9)

^aDefined as low C3 or C4 and high anti-dsDNA ≥ 30 IU/ml. ^bFor those with available scores.

BILAG: British Isles Lupus Assessment Group of SLE Clinics; BMI: body mass index; C: complement; dsDNA: double-stranded DNA; MITT: modified intent-to-treat; PGA: Physician's Global Assessment; SD: standard deviation; SELENA-SLEDAI: Safety of Estrogen in Lupus National Assessment Systemic Lupus Erythematosus Disease Activity Index; SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLE: systemic lupus erythematosus.

Table 2 Study withdrawals by study year (MITT population)

	Overall ^a (<i>N</i> = 998)	Year 0–1 (<i>N</i> = 998)	Year 1–2 (<i>N</i> = 955)	Year 2–3 (<i>N</i> = 861)	Year 3–4 (<i>N</i> = 734)	Year 4–5 (<i>N</i> = 655)	Year 5–6 (<i>N</i> = 531)
<i>n</i> (%)	427 (42.8)	43 (4.3)	94 (9.8)	115 (13.4)	62 (8.4)	48 (7.3)	37 (7.0)
AEs, <i>n</i> (%)	85 (8.5)	15 (1.5)	15 (1.6)	20 (2.3)	18 (2.5)	13 (2.0)	2 (0.4)
Investigator decision, <i>n</i> (%) ^b	48 (4.8)	4 (0.4)	6 (0.6)	10 (1.2)	4 (0.5)	2 (0.3)	11 (2.1)
Lack of compliance, <i>n</i> (%)	12 (1.2)	1 (0.1)	1 (0.1)	5 (0.6)	1 (0.1)	2 (0.3)	2 (0.4)
Lack of efficacy, <i>n</i> (%)	16 (1.6)	2 (0.2)	5 (0.5)	5 (0.6)	1 (0.1)	1 (0.2)	2 (0.4)
Lost to follow-up, <i>n</i> (%)	25 (2.5)	1 (0.1)	6 (0.6)	7 (0.8)	5 (0.7)	2 (0.3)	1 (0.2)
Other, <i>n</i> (%) ^c	70 (7.0)	4 (0.4)	15 (1.6)	14 (1.6)	14 (1.9)	8 (1.2)	6 (1.1)
Protocol violation, <i>n</i> (%)	3 (0.3)	0	2 (0.2)	0	0	1 (0.2)	0
Patient request, <i>n</i> (%)	168 (16.8)	16 (1.6)	44 (4.6)	54 (6.3)	19 (2.6)	19 (2.9)	13 (2.4)

^aIncludes patients who withdrew beyond study years 5–6. ^bIncludes one individual who reported an AE leading to discontinuation but the investigator recorded reason for withdrawal as “investigator decision.” ^cIncludes three patients who died during the study period, and investigator recorded reason for withdrawal as “Other.”

AE: adverse event; MITT: modified intent-to-treat; *N*: number of patients who were in the study at the start of the study year.

years 5–6 (MITT study year 5–6 population; *n* = 241) was 0.2 (0.44) (Figure 2(b)); 211 (87.6%) of these patients had no change in SDI score at study years 5–6, 24 (10.0%) had an SDI increase of 1, five (2.1%) had an increase of 2, and one

(0.4%) had an increase of 3. In patients with organ damage at baseline, the mean (SD) SDI change at study years 5–6 (*n* = 162) was 0.2 (0.53) (Figure 2(b)); 132 (81.5%) of these patients had no change in SDI score at study years 5–6, 22 (13.6%)

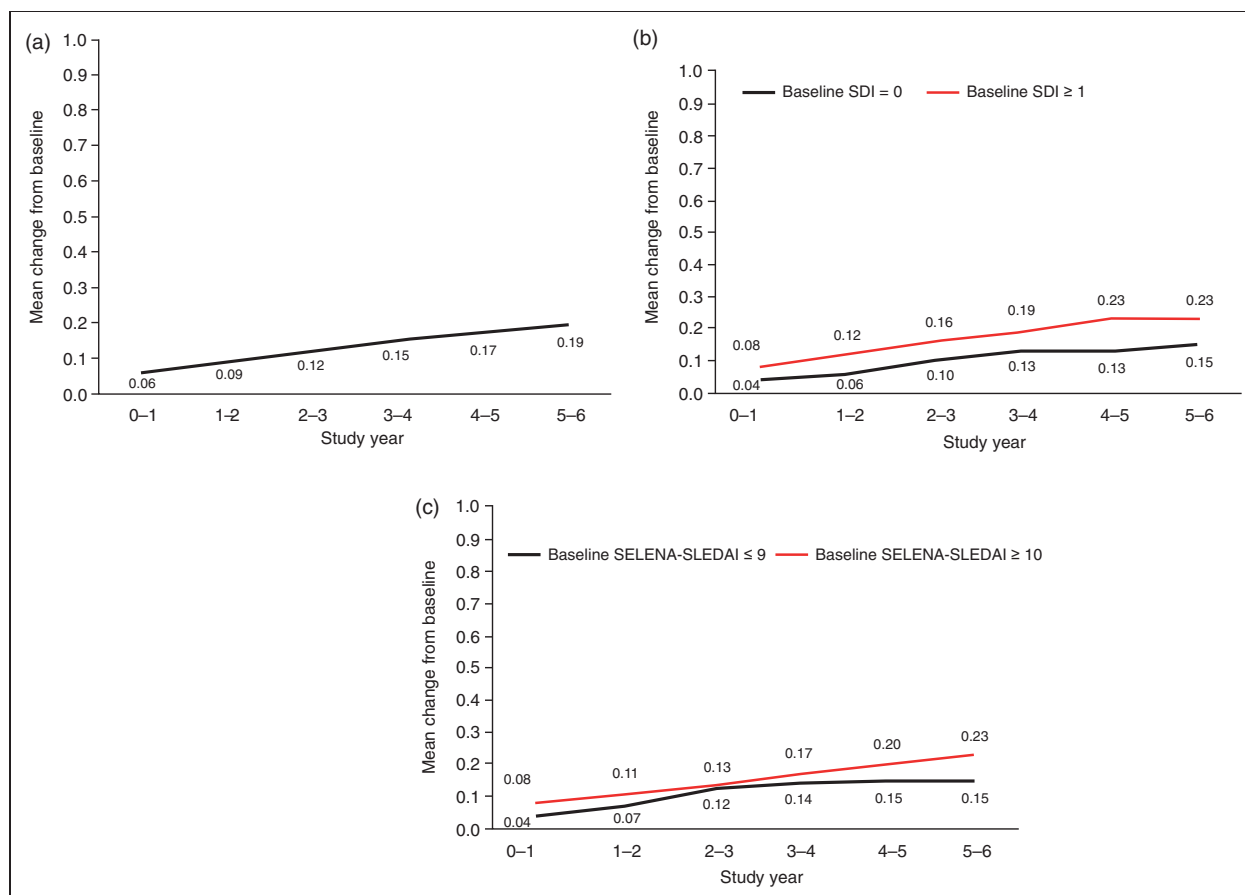


Figure 2 Change from baseline in total SDI score (a), by baseline SDI score 0 or ≥ 1 (b) and by baseline SELENA-SLEDAI ≤ 9 or ≥ 10 (c) (all MITT population). SELENA-SLEDAI: Safety of Estrogen in Lupus National Assessment-Systemic Lupus Erythematosus Disease Activity Index; SDI: Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) Damage Index; MITT: modified intent-to-treat.

Table 3 Change from baseline in SDI score summarized by study year (MITT)

	Year 0-1	Year 1-2	Year 2-3	Year 3-4	Year 4-5	Year 5-6
Decrease ^a	33	33	31	26	23	18
<i>n</i>	941	887	785	677	565	403
No change, <i>n</i> (%)	896 (95.2)	821 (92.6)	702 (89.4)	591 (87.3)	488 (86.4)	343 (85.1)
+1, <i>n</i> (%)	40 (4.3)	58 (6.5)	69 (8.8)	68 (10.0)	59 (10.4)	46 (11.4)
+2, <i>n</i> (%)	3 (0.3)	6 (0.7)	13 (1.7)	18 (2.7)	16 (2.8)	13 (3.2)
+3, <i>n</i> (%)	2 (0.2)	2 (0.2)	1 (0.1)	0	2 (0.4)	1 (0.2)
Missing	2	2	2	2	2	0
Mean change (SD)	0.06 (0.267)	0.09 (0.325)	0.12 (0.388)	0.15 (0.428)	0.17 (0.470)	0.19 (0.481)

^aNumber of patients who had at least one decrease in any item level SDI score at any time and who had a SDI assessment during the study year. SDI score should not decrease over time, therefore these patients were excluded from this analysis.

MITT: modified intent-to-treat; SD: standard deviation; SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

had an SDI increase of 1, and eight (4.9%) had an SDI increase of 2. Similarly (Figure 2(c)), the mean (SD) SDI change from baseline at study years 5-6 (MITT study year 5-6 population) was 0.2 (0.46)

for patients who had baseline SELENA-SLEDAI score ≥ 10 ($n = 170$) and 134 (78.8%) patients had no change in SDI score; the mean change was 0.2 (0.49) for those with SELENA-SLEDAI score

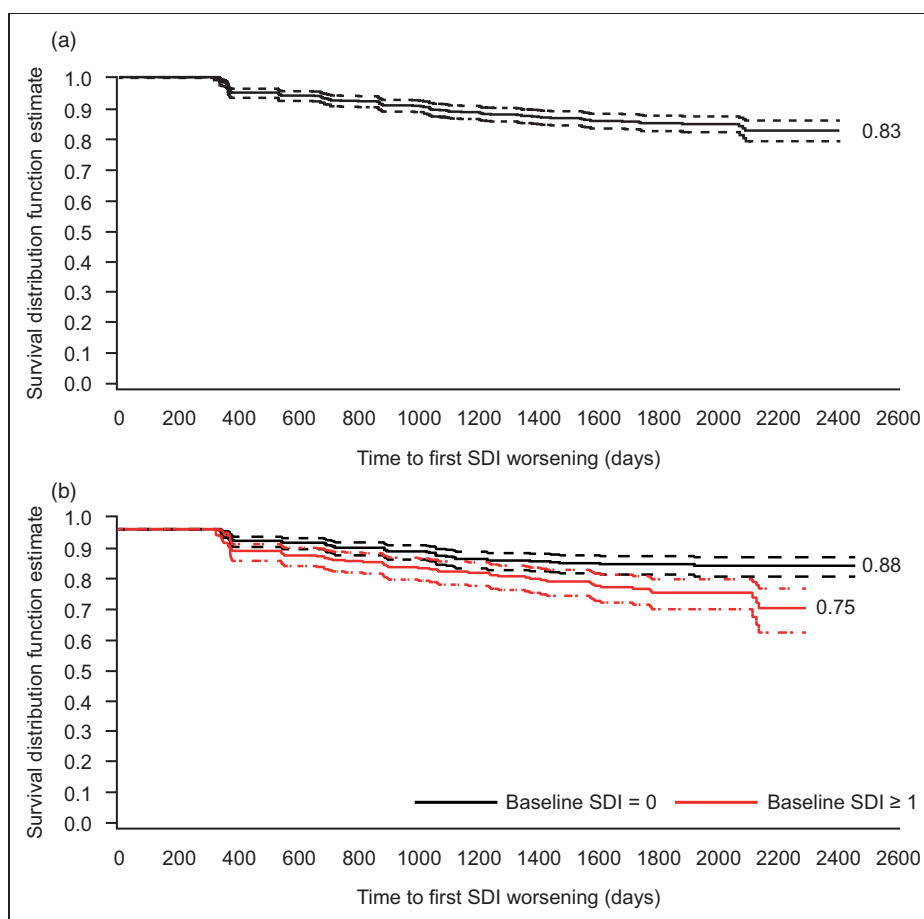


Figure 3 Time to first SDI worsening (a) and by baseline SDI score 0 or ≥ 1 (b) (all MITT population). Patients who withdrew/completed prior to their first worsening are censored at their final SDI assessment date prior to study exit/date cutoff. Patients who withdrew prior to having a post-baseline SDI assessment are censored at day 0 (treatment start date). Patients who had decreases were not included. SDI: Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) Damage Index; MITT: modified intent-to-treat.

≤ 9 ($n=233$) and 209 (89.7%) patients had no change in SDI score.

In the five-year completer subpopulation at study years 5–6 ($n=372$), the mean (SD) change from baseline in SDI (0.2 (0.47)) was comparable to the MITT population. A total of 317 (85.2%) five-year completers had no SDI change, 44 (11.8%) had an SDI increase of 1, 10 (2.7%) had an SDI increase of 2, and one (0.3%) had an increase of 3. In the serologically active subpopulation with SDI data available at study years 5–6 ($n=194$), the mean (SD) change from baseline in SDI (0.2 (0.46)) was also comparable to the MITT population; 166 (85.6%) of serologically active patients had no SDI change, 22 (11.3%) had an SDI increase of 1, and six (3.1%) had an SDI increase of 2.

At study years 5–6, the organ systems in which new damage occurred most frequently were ocular

(19 (4.7%) had an increase of 1), musculoskeletal (11 (2.7%) had an increase of 1, and four (1.0%) had an increase of 2) and diabetes (seven (1.7%) had an increase of 1).

Time to first SDI worsening

The probability of not having a worsening in SDI score was 0.83 (95% confidence interval (CI): 0.79, 0.86) and the median (IQR) time to first worsening was 677 (364–1045) days (MITT; $n=117$) (Figure 3(a)).

In a post hoc analysis of patients (MITT) with worsening organ damage, the median time to first worsening was 679 days for patients with no organ damage at baseline ($n=53$) and 672 days for those with organ damage at baseline ($n=64$). The probability of not having a worsening in SDI score was 0.88 (95% CI: 0.85, 0.91) in those with no baseline

damage and 0.75 (95% CI: 0.67, 0.81) in those with baseline damage (Figure 3(b)).

Safety

The majority (96.5%, MITT) of patients experienced an AE any time post baseline; the incidence of AEs decreased from 87.4% to 52.7% across study years. A total of 313 patients (31.4%) experienced a serious AE (SAE); the highest incidence in a single study year was 10.8% (study year 0–1) and the incidence tended to decrease over time to 5.6% (study year 5–6) (Table 4). Overall, 433 (43.4%) patients experienced a drug-related AE, and this also decreased over time (Table 4). The most commonly reported drug-related AE groupings were infections/infestations (282, 28.3%) and gastrointestinal disorders (139, 13.9%). AEs of special interest are summarized in Table 4; opportunistic infection was reported for 23 (2.3%) patients—four cases of which were serious, and herpes zoster infection was reported for 87 patients (8.7%)—seven cases were judged serious (Table 4). No completed suicides were reported as such during the study; one polydrug toxicity resulting in death was later adjudicated as a suicide by GSK physicians.

Serologically active patients had AE incidences similar to the MITT population (data not shown).

Eleven deaths were recorded during the study period and three additional deaths occurred after study exit. Causes of death included pneumonia (three) and septic shock (one), pancreatitis (one), thrombocytopenia (one), cardiogenic shock (one, possibly treatment related as per investigator), pulmonary hemorrhage (one), hypertensive heart disease (one), polydrug toxicity (one), stroke (one), sepsis (one), intracranial hemorrhage (one) and cardiac arrest (one).

Discussion

In two randomized, controlled studies, belimumab was effective as add-on therapy to SoC in patients with active autoantibody-positive SLE.^{14,15} In this analysis of two ongoing continuation studies of patients treated with belimumab plus SoC, we observed low rates of organ damage accrual and no new safety issues.

The primary aim of initial clinical studies of any novel therapeutic agent in SLE is to demonstrate short-term efficacy in controlling inflammatory disease activity. We used the SDI, a validated and accepted instrument, to measure the potential for belimumab to prevent or attenuate long-term

irreversible organ damage. A low overall progression of damage within our cohort was observed that was lower than that reported in other cohorts.^{5,10,11} The mean change from baseline in total SDI score was 0.2 at years 5–6, and 85.1% of patients had no change in SDI score. In contrast, within the SLICC inception cohort, 178/348 (51.1%) patients had at least one new item of damage over six years;⁵ however, the inception cohort may have included patients who progressed rapidly early in their disease course, who could have been missed in our study. Forty-two percent of patients in the Tromso cohort developed damage over five years,¹¹ and in the Lupus in Minorities: Nature versus Nurture (LUMINA) cohort the mean (SD) SDI score increased from 0.8 (0.1) to 2.4 (0.4) over five years.¹⁰ An important difference between our cohort and observational cohorts is that the full spectrum of patients with SLE are included in observational cohorts, including those with predominant lupus nephritis and central nervous system (CNS) disease. Both of these manifestations may be associated with higher rates of damage accrual and were exclusion criteria for the BLISS studies.^{14–17} A lower rate of damage accrual may therefore be expected in our population. However, patients with previous renal activity could enroll in the parent studies; approximately 16% of BLISS patients had renal involvement by SELENA-SLEDAI, 10.6% had a British Isles Lupus Assessment Group (BILAG) renal A or B score, and 20.4% had proteinuria > 0.5 g/24 h,^{14,15,18} though these populations may not be reflective of the MITT population in our long-term extension study.

There is no control group of patients who received only SoC in our study. Despite this limitation, the study indicates a low rate of organ damage accrual over time. Further, we explored damage accrual in patients with high and low levels of disease activity at baseline (SELENA-SLEDAI score ≤ 9 and ≥ 10) and observed similar rates of damage accrual between these subgroups. This was unexpected, as previous studies have shown that higher disease activity and/or major flares affect the risk of future damage.^{5,19,20} We hypothesize that exposure to belimumab plus SoC may attenuate damage in a damage-prone population. Observational cohorts consistently find significantly greater rates of damage development in patients with pre-existing damage compared with those without.^{10,12,19} In contrast, while there was a greater probability of new damage in our patients who had existing damage, the absolute rate of damage was low compared with other cohorts.⁵

Table 4 Incidence of AEs and AEs of special interest (MITT) by study year

	<i>Any time post-baseline^a</i> (N = 998)	<i>Year 0–1</i> (N = 998)	<i>Year 1–2</i> (N = 955)	<i>Year 2–3</i> (N = 861)	<i>Year 3–4</i> (N = 734)	<i>Year 4–5</i> (N = 655)	<i>Year 5–6</i> (N = 531)
At least one AE	963 (96.5)	872 (87.4)	722 (75.6)	634 (73.6)	527 (71.8)	431 (65.8)	280 (52.7)
At least one drug-related AE	433 (43.4)	283 (28.4)	167 (17.5)	127 (14.8)	96 (13.1)	70 (10.7)	46 (8.7)
At least one serious AE	313 (31.4)	108 (10.8)	88 (9.2)	92 (10.7)	66 (9.0)	43 (6.6)	30 (5.6)
AEs of special interest							
Malignant neoplasms ^b	26 (2.6)	4 (0.4)	3 (0.3)	8 (0.9)	7 (1.0)	2 (0.3)	0
Infusion and hypersensitivity reactions ^c	45 (4.5)	30 (3.0)	18 (1.9)	11 (1.3)	9 (1.2)	9 (1.4)	5 (0.9)
All infections of special interest	117 (11.7)	38 (3.8)	29 (3.0)	20 (2.3)	26 (3.5)	16 (2.4)	12 (2.3)
Serious	17 (1.7)	6 (0.6)	3 (0.3)	1 (0.1)	6 (0.8)	0	1 (0.2)
Opportunistic infections	23 (2.3)	5 (0.5)	6 (0.6)	3 (0.3)	2 (0.3)	2 (0.3)	4 (0.8)
Serious	4 (0.4)	2 (0.2)	1 (0.1)	0	0	0	1 (0.2)
Herpes zoster	87 (8.7)	28 (2.8)	17 (1.8)	13 (1.5)	15 (2.0)	10 (1.5)	8 (1.5)
Serious	7 (0.7)	4 (0.4)	1 (0.1)	0	2 (0.3)	0	0
Sepsis	12 (1.2)	5 (0.5)	1 (0.1)	2 (0.2)	3 (0.4)	1 (0.2)	2 (0.4)
Serious	10 (1.0)	5 (0.5)	1 (0.1)	2 (0.2)	2 (0.3)	1 (0.2)	1 (0.2)
Depression ^d	154 (15.4)	65 (6.5)	39 (4.1)	33 (3.8)	19 (2.6)	10 (1.5)	10 (1.9)
Serious suicide/self-injury ^e	4 (0.4)	0	0	2 (0.2)	0	2 (0.3)	0

^aIncludes data beyond the study years 5–6. ^bAll malignant neoplasms, including non-melanoma skin cancer. ^cPer a modified anaphylactic reaction SMQ algorithmic search, defined as at least one AE coding to a Category A (core anaphylactic terms, modified to add the following terms: “infusion-related reaction,” “drug hypersensitivity,” and “hypersensitivity”), or two AEs, one coding to a Category B preferred term (upper airway/respiratory terms) and the other coding to a Category C (angioedema/urticaria/pruritis/flush terms) or two AEs, one coding to a Category D preferred term (cardiovascular/hypotension terms) and the other coding to either a Category B preferred term or to a Category C preferred term, occurring on or within three days of infusion. ^dFrom the depression SMQ. ^eFrom the suicide/self-injury SMQ; no completed suicides reported though one event of polydrug toxicity was adjudicated by GSK physicians as suicide.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; MITT: modified intent-to-treat; SMQ: standardized MedDRA query.

We also conducted a post hoc sensitivity analysis to examine whether patients who withdrew from the studies did so because of organ damage; results were similar to those in the overall MITT population, suggesting that organ damage was not a key reason for study withdrawal.

Potential mechanisms for the lower rate of damage accrual observed include better overall control of inflammatory disease activity, which could be due to lower steroid doses and reductions in flares. Disease flares contribute to future damage^{19,20} and belimumab has been shown in secondary analyses of pooled BLISS study data to reduce severe flares.^{14,15} Corticosteroid use is also a key driver of future damage,^{5,21,22} and several damage items have been shown to be strongly linked to steroid use.²³ In secondary analyses of pooled BLISS study data, belimumab use resulted in a higher proportion of patients with SLE achieving a stable steroid dose of < 7.5 mg/day prednisone, compared with SoC.^{14,15} The long-term effect of belimumab on damage accrual may be partly mediated through improving disease stability and/or steroid-sparing effects.

Our study enabled assessment of long-term safety in a large population continuing on belimumab. In general, the long-term safety was consistent with the known safety profile of belimumab,^{14,15} and the incidence of SAEs of special interest was

low and either remained stable or decreased over time. Although the “any-time post-baseline” incidences of opportunistic infections and depression reported here are higher than have been reported previously, in the Phase 2 and Phase 3 studies (0.3% vs 2.3% and 5.8% vs 15.4%, respectively),²⁴ this reflects the longer duration of the present analysis. When considering each yearly interval separately, the rates are consistent with the shorter-term studies, and the incidences either remain stable or decrease over time.

There were 85/998 (8.5%) study withdrawals due to AEs, up to data cutoff. In the only other long-term continuation study of belimumab, following a Phase II study that examined safety of belimumab plus SoC over seven years, the rate/100 patient-years of discontinuations because of AEs was 1.9–6.4% over each study year.²⁵ However, comparison between these studies is limited due to differing study designs and populations. In the long-term Phase II extension study, AEs were measured in rates over calendar-year intervals, and patients were slightly older at study entry (mean: 43 vs 39 years), had a slightly longer disease duration (mean: 8.8 vs 6.7 years), a higher mean SELNASLEDAI (9.2 vs 8.2), and a higher percentage had at least one BILAG A or two BILAG B scores (64 vs 46%).

This study has several strengths and limitations. We studied a large global population of patients with active moderate to severe SLE up to study years 5–6. The sensitivity analysis demonstrated that the infrequent reports of SDI decreases had little impact on the overall results or conclusions, indicating a low error rate. The entry criteria for the BLISS studies are comparable to a number of other non-renal lupus studies.^{26,27} This provides important data on damage accrual among a subset of patients with lupus with active disease but without recent lupus nephritis and/or CNS involvement. Damage accrual data in lupus have traditionally come from observational cohorts, which include all-comers with disease. We recognize that our studies are ongoing, open-label studies with no placebo (SoC) data for comparison; therefore, results should be interpreted with some caution. Nevertheless, the comparable rates of damage accrual in patients with higher and lower disease activity, and between those with and without pre-existing damage, raise the hypothesis that belimumab plus SoC may help to control disease activity and/or spare corticosteroids, which overall may result in less long-term damage in SLE. It is worth noting that both belimumab dosage exposures were pooled and approximately one-third of patients were initially receiving a lower dose of 1 mg/kg. Finally, the continuation studies were designed to have 48-week years and as such do not align with calendar years. Thus, we presented data using a study year 5–6 window, where the majority of SDI assessments were performed more than five years after patients' first dose of belimumab, and a five-year completer analysis. Over this long-term period, these safety and damage data retain validity.

In conclusion, patients with moderate to severe SLE treated with belimumab plus SoC up to study years 5–6 had a low incidence of organ damage accrual, and no new safety issues were identified. Importantly, patients with pre-existing organ damage, who were therefore at higher risk for additional damage, also experienced low overall rates of damage. The hypothesis that belimumab may have beneficial effects on long-term damage development is one that now requires further investigation.

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