











ORIGINAL RESEARCH

Long-term open-label continuation study of the safety and efficacy of belimumab for up to 7 years in patients with systemic lupus erythematosus from Japan and South Korea

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ABSTRACT

Objectives To evaluate the long-term safety and efficacy of belimumab in patients with systemic lupus erythematosus (SLE) from Japan and South Korea.

Methods In this phase III, open-label continuation study (BEL114333; NCT01597622), eligible completers of BEL113750 (NCT01345253) or BEL112341 (NCT01484496) received intravenous belimumab 10 mg/kg every 28 days for ≤7 years. Primary endpoint was safety. Secondary endpoints: SLE Responder Index (SRI)4 response rate, proportion of patients meeting individual SRI4 criteria, SLE flares and prednisone use. Analyses were based on observed data from the first belimumab exposure (either in parent or current study) through to study end.

Results Of 142 enrolled patients who received belimumab, 73.2% completed the study. The study population comprised patients with moderate SLE, mean (SD) Safety of Estrogens in Lupus Erythematosus National Assessment-SLE Disease Activity Index (SELENA-SLEDAI) baseline score of 9.3 (3.9) and 98.6% receiving corticosteroids. Most patients (97.9%) experienced adverse events (AEs); 33.8% experienced serious AEs. Increase in SRI4 (Year 1, Week 24: 47.8%; Year 6, Week 48: 68.2%) and SELENA-SLEDAI responders suggested reductions in disease activity. Proportions of patients with no worsening in Physician Global Assessment/no new organ damage remained stable throughout. Severe SLE flares occurred in 14.8% of patients. Among patients with baseline prednisone-equivalent dose >7.5 mg/day (n=81), the median (min, max) number of days anytime post-baseline that the daily dose was ≤7.5 mg/day or had been reduced by 50% from baseline was 584 (0, 2267).

Conclusions Favourable safety profile and treatment responses were maintained for ≤7 years in patients with SLE from Japan and South Korea.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a systemic autoimmune disorder characterised

Key messages

What is already known about this subject?

- Belimumab is a recombinant, humanised immunoglobulin G1 lambda (IgG1λ) monoclonal antibody that binds to and inhibits the action of soluble human B-lymphocyte stimulator (BLyS) protein.
- In double-blind, placebo-controlled trials of patients with systemic lupus erythematosus (SLE), intravenous belimumab treatment reduces disease activity and new organ damage accrual and has an acceptable safety and tolerability profile.
- Long-term data on the efficacy and safety of belimumab are limited in Japanese and South Korean populations.

What does this study add?

- Belimumab was well tolerated and appeared to reduce disease activity and slow organ damage progression; also, it contributed to corticosteroid dose reduction over the longer term (up to 7 years) in patients with SLE in Japan and South Korea.

How might this impact on clinical practice or future developments?

- The results of the presented analyses support a positive benefit–risk profile of treatment with belimumab as an add-on to standard therapy in patients with active SLE in Japan and South Korea.

by loss of immune tolerance against nuclear autoantigens.^{1–3} Patients with SLE have elevated levels of B-lymphocyte stimulator (BLyS) protein, which promotes abnormal B-cell activation and differentiation.^{4–6} B cells produce autoantibodies targeting nuclear components, such as anti-double-stranded deoxyribonucleic acid (anti-dsDNA), which can lead to irreversible organ damage and early mortality.⁷

The prevalence and severity of SLE are greater in non-Caucasian populations (Hispanic, African descendant and Asian) than in Caucasian populations,⁸ suggesting a potential genetic predisposition to SLE in these groups. In Japan, SLE is estimated to affect 4.3–37.7 people per 100 000 and in South Korea the estimated prevalence is 20.6–26.5 people per 100 000.^{9 10} Despite the availability of various standard therapies, such as corticosteroids and immunosuppressants, many patients continue to experience a considerable disease burden.^{11–13} In addition, prolonged use of such therapies is often associated with frequent adverse events (AEs); thus, there remains a need for therapeutic alternatives, particularly in patients with high disease activity.^{14 15}

Belimumab is a recombinant, humanised immunoglobulin G1 lambda (IgG1 λ) monoclonal antibody (mAb) that binds to BLYS, antagonising its biological activity.¹⁶ Intravenous (IV) belimumab 10 mg/kg is approved in Europe, the USA, Japan and South Korea for the treatment of patients with active autoantibody-positive SLE receiving standard therapy.^{17–20} The efficacy and safety of belimumab in patients with SLE were examined in previous phase III trials, which demonstrated that belimumab-treated patients have reductions in disease activity, new organ damage accrual and corticosteroid dose.^{21–24} Long-term continuation studies involving 7–13 years of belimumab treatment have confirmed that efficacy and acceptable safety and tolerability profile were maintained over this time.^{25–27} However, limited data exist on the long-term efficacy and safety of belimumab

in patients with SLE from Japan and South Korea. Therefore, the objective of this continuation study was to evaluate the long-term safety, tolerability and efficacy of belimumab in patients with SLE from Japan and South Korea.

METHODS

Study design

This was a phase III, open-label, multicentre, continuation study of belimumab (GlaxoSmithKline Study BEL114333; ClinicalTrials.gov identifier NCT01597622) plus standard therapy conducted at 27 study centres across Japan and South Korea in patients with SLE who completed the parent studies, the 52-week double-blind phase of the BEL113750 (NCT01345253) study receiving IV belimumab in Japan and South Korea,²⁴ or the subcutaneous (SC) open-label phase of the BEL112341 (NCT01484496) study in Japan (figure 1).²⁸ Eligible patients entering this study received belimumab 10 mg/kg IV infused over 1 hour every 28 days for up to 7 years plus standard therapy, irrespective of their randomised treatment in the parent studies. Patients were scheduled to receive their first belimumab dose 4 weeks (range 2–8 weeks) after their last IV dose in study BEL113750 or the first dose of IV belimumab 1 week (\pm 1 week) after the last dose of SC belimumab in study BEL112341. Patients continued to receive belimumab unless specific stopping criteria occurred (online supplemental materials).

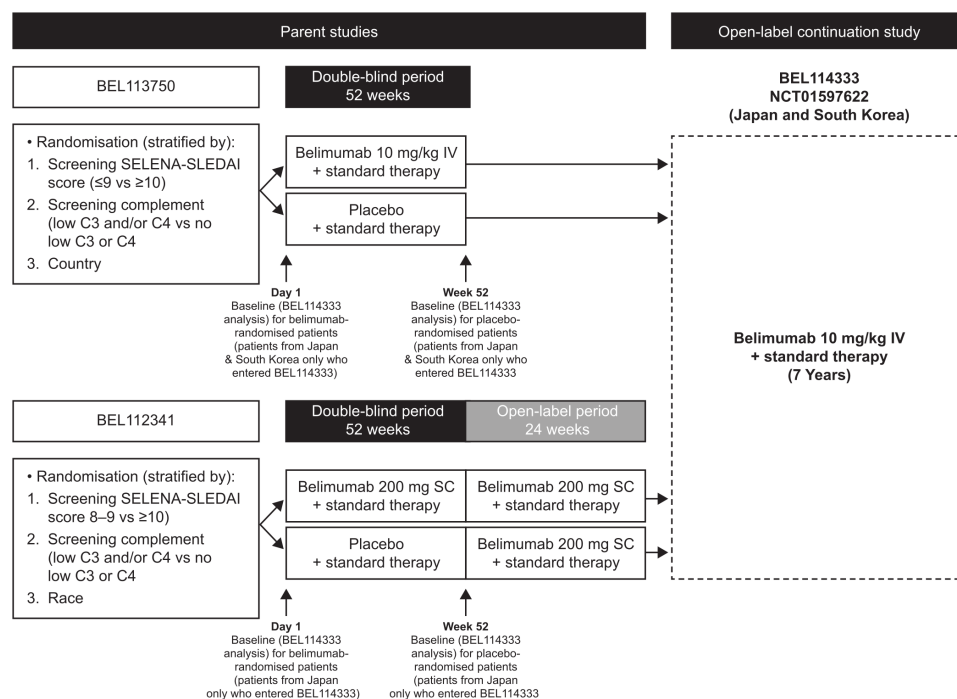


Figure 1 Study design.

Note: Due to the additional 6-month open-label extension for SC patients entering BEL114333, there is a 6-month offset in the data capture between the parent studies.

C3/C4, complement 3/4; SC, subcutaneous; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment-SLE Disease Activity Index; SLE, systemic lupus erythematosus.

Blinding

BEL113750 study blinding was maintained by the sponsor until all double-blind data were locked, and clinical sites remained blinded to BEL113750 treatment until the double-blind results were publicly disclosed. Patients from the open-label extension of the BEL112341 study were already unblinded.

Patients

Eligible patients had completed study BEL113750 or the open-label phase of study BEL112341 in study centres in Japan or South Korea. Full eligibility criteria for the parent studies have been previously published.^{24–28} Patients had to be on a stable SLE treatment regimen for ≥ 30 days prior to Day 0 of both parent studies, consisting of any of the following (alone or in combination): prednisone-equivalent dose (0–40 mg/day when used in combination with other SLE treatment or 7.5–40 mg/day when used alone), antimalarials, non-steroidal anti-inflammatory drugs or any other immunosuppressants or immunomodulatory therapy (eg, methotrexate, azathioprine, leflunomide, mycophenolate, mizoribine, calcineurin inhibitors, sirolimus, oral cyclophosphamide, 6-mercaptopurine or thalidomide), at the discretion of the investigator (online supplemental materials).

Further key eligibility criteria and permissible and prohibited medications are listed in the online supplemental materials.

Endpoints and assessments

The primary endpoint was safety, which was assessed by the incidence of AEs, serious AEs (SAEs) and AEs of special interest (AESIs), clinical laboratory tests and immunogenicity throughout the study. Treatment-emergent AEs were defined as any AE that occurred or pre-existing event that worsened in severity or relatedness after receipt of the first belimumab dose (refer to the Statistical analysis section). AEs were assessed at each infusion visit and other safety endpoints were monitored at regular intervals, until the 16-week follow-up visit (post final belimumab dose). For further information refer to online supplemental materials.

The key secondary efficacy endpoint was observed proportion of SLE Responder Index (SRI)4 responders (defined as a ≥ 4 -point reduction from baseline in Safety of Estrogens in Lupus Erythematosus National Assessment-SLE Disease Activity Index (SELENA-SLEDAI) score, no worsening in Physician Global Assessment (PGA; < 0.3 -point increase from baseline) and no new British Isles Lupus Assessment Group (BILAG) 1A/2B organ domain scores) assessed at scheduled 24 weeks and 4 weeks post-final belimumab dose (exit visit).

Additional secondary/other efficacy endpoints included the proportion of patients meeting each of the three SRI4 response component criteria individually; median time to first severe SELENA-SLEDAI Flare Index (SFI) flare; proportion of patients experiencing SFI flare, BILAG 1A/2B flare (≥ 1 new 1A or ≥ 2 new 2B

scores) and renal flare at any time post first dose of belimumab; the cumulative number of days when prednisone dose was ≤ 7.5 mg/day and/or reduced by 50% from baseline and change from baseline in SELENA-SLEDAI and PGA scores. Efficacy endpoints were assessed at scheduled 24-week visits and exit visit. Change from baseline in Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) Damage Index (SDI) was assessed at Week 48 annually and at exit visit.

Change from baseline in serum IgG, anti-dsDNA auto-antibodies, complement (C3, C4), B cells and B-cell subsets was also assessed. B-cell subsets were analysed centrally in patients from selected sites in Japan only.

AEs coding and the definition of SFI flares are provided in online supplemental materials.

Statistical analysis

Enrolment in this study was dependent on the number of patients in Japan and South Korea who completed the BEL113750 and BEL112341 studies; therefore, no sample size calculations were performed. Baseline was defined as the last available value prior to belimumab initiation: Day 1 of the parent study for patients randomised to belimumab and Week 52 of the parent study for patients randomised to placebo (figure 1). As such, exposure data to belimumab during parent studies were included for patients who received their first dose in the parent study and subsequently enrolled in BEL114333. Analyses were descriptive, based on observed data, and summarised relative to baseline. No follow-up data were collected post study. All data summaries and analyses were performed using SAS software, V.9.3 or higher (SAS Institute).

The safety population was defined as all patients who received ≥ 1 dose of belimumab during the BEL114333 study. AEs were summarised at any time post first dose of belimumab and by year of belimumab treatment, starting from first belimumab dose (baseline). All safety and efficacy endpoints were assessed in the safety population. Exit visits were slotted to the next scheduled visit for each efficacy endpoint.

Data from patients who received SC belimumab in the BEL112341 study and who received IV belimumab in the BEL113750 study were combined and analysed together. Data for the SDI, IgG and B cells and B-cell subsets were presented by parent study and by the timepoints at which they were collected, because of differences in data collection timepoints.

Patient and public involvement

This study did not involve patients or the public in the design or implementation of the study or the dissemination of its results.

RESULTS

Patient disposition and baseline characteristics

The first patient was enrolled in the continuation study (BEL114333) on 11 June 2012, and the last patient last

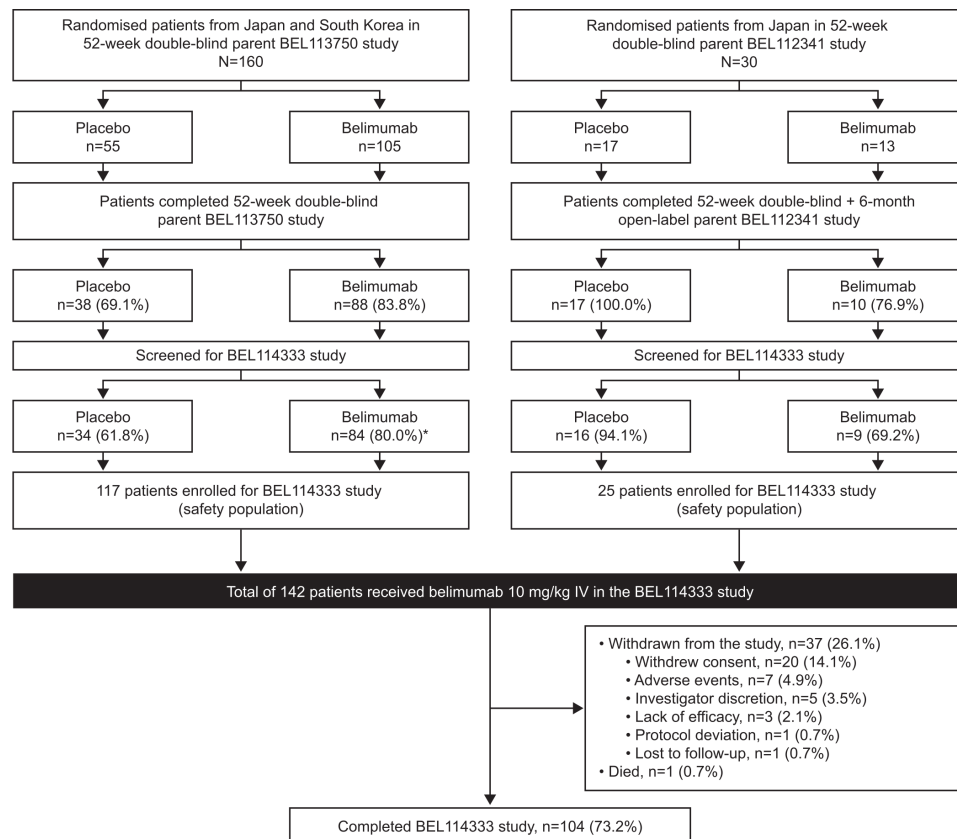


Figure 2 Patient disposition.

*One screened patient in the belimumab treatment group did not enter BEL114333 due to a serious AE of chronic pancreatitis which started during the parent Study BEL113750. Note: Study completers included all patients who transferred to a different protocol or who were still participating in the study at the time of the sponsor decision to close the study when belimumab became commercially available in Japan and South Korea. There were eight adverse events (AEs) resulting in the withdrawal of seven patients from the study: spontaneous abortion, ALT increased, angiocentric lymphoma, AST increased, asphyxia, pleurisy, bacterial pneumonia and skin ulcer.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; IV, intravenous.

visit for this study was on 13 September 2018. Of the 190 patients from Japan and South Korea who were randomised in the parent studies, 153 completed the respective parent studies and 142 (Japan: n=72; South Korea: n=70) enrolled in the continuation study and were included in the safety population. In total, 73.2% (104/142) of patients completed the continuation study; 1 patient died (0.7%) and 37 (26.1%) withdrew from the study, mainly because of withdrawal of consent (14.1%) and AEs (4.9%) (figure 2). The median (min, max) duration of belimumab exposure was 1171 (87, 2432) days, with a total belimumab exposure of 458.9 patient-years, including exposure during parent studies.

Demographic and baseline disease characteristics are presented in table 1. A total of 14.1% of patients had no BILAG domain involvement (A or B) and 51.4% of patients had a baseline SELENA-SLEDAI Score ≤ 9 (table 1). The mean (SD) baseline SELENA-SLEDAI Score was 9.3 (3.9). Patients who were randomised to placebo in the parent studies and subsequently entered in BEL114333, had lower mean SELENA-SLEDAI and PGA scores at baseline (prior to first dose of belimumab)

compared with patients randomised to belimumab (online supplemental table 1).

Most patients (98.6%) received corticosteroids at baseline, 40.8% received antimalarials and 76.1% received immunosuppressants, with tacrolimus being the most commonly received (table 1).

Concomitant SLE medications permitted during the study are shown in online supplemental table 2.

Safety

Overall, 97.9% (139/142) of patients experienced ≥ 1 treatment-emergent AE and most AEs were mild or moderate in severity. The most frequent AEs included nasopharyngitis (60.6%), headache (28.2%) and cough, herpes zoster and viral upper respiratory infection (each 18.3%) (table 2). AE rate for any event at any time post first dose of belimumab was 477.2 events/100 patient-years (table 3).

Serious treatment-emergent AEs were reported in 33.8% (48/142) of patients, with the most frequently reported SAEs by system organ class being infections and infestations. Cellulitis, contusion and herpes zoster were

Table 1 Patient demographics and baseline clinical characteristics (safety population; N=142)

	Total (N=142)
Country, n (%)	
Japan	72 (50.7)
South Korea	70 (49.3)
Female, n (%)	129 (90.8)
Mean age (SD), years	34.6 (9.3)
Ethnicity, n (%)	
Hispanic or Latino	1 (0.7)
Non-Hispanic or non-Latino	141 (99.3)
Mean BMI (SD), kg/m ²	21.8 (3.4)
Mean SLE disease duration (SD), years	8.7 (6.6)
BILAG organ domain involvement*, n (%)	
≥1A or 2B	64 (45.1)
≥1A	18 (12.7)
≥1B	116 (81.7)
Neither A nor B	20 (14.1)
BILAG organ system involvement (A or B scores), n (%)	
General	7 (4.9)
Mucocutaneous	77 (54.2)
Neurological	1 (0.7)
Musculoskeletal	40 (28.2)
Cardiovascular and respiratory	1 (0.7)
Vasculitis	22 (15.5)
Renal	28 (19.7)
Haematology	31 (21.8)
Mean SELENA-SLEDAI Score (SD)	9.3 (3.9)
SELENA-SLEDAI category, n (%)	
≤9	73 (51.4)
≥10	69 (48.6)
SELENA-SLEDAI Flare Index**†, n (%)	
≥1 flare	27 (19.0)
≥1 severe flare	4 (2.8)
Mean PGA (SD)	1.2 (0.6)
SDI Score	
Mean (SD)	0.5 (0.8)
Median (min, max)	0.0 (0, 4)
ANA‡	
Positive (≥0.80 index or ≥80 titre), n (%)	140 (98.6)
Anti-dsDNA	
Positive (≥30IU/mL), n (%)	118 (83.1)
Complement level, n (%)	
Low C3 (<90 mg/dL) and/or low C4 (<10 mg/dL)	121 (85.2)
No low C3 or C4	21 (14.8)
Mean proteinuria level (SD), g/24 hours	0.7 (1.0)
Proteinuria category (g/24 hours), n (%)	
≤0.5	95 (66.9)
>0.5	47 (33.1)
>0.5 to <1	13 (9.2)
1 to <2	19 (13.4)
≥2	15 (10.6)

Continued

Table 1 Continued

	Total (N=142)
Medication at baseline	
Corticosteroids, n (%)	140 (98.6)
Mean daily prednisone§ dose (SD), mg/day	10.1 (5.9)¶
Median daily prednisone§ dose (IQR), mg/day	10.0 (6.3, 12.5)¶
Antimalarials**, n (%)	58 (40.8)
Hydroxychloroquine	32 (22.5)
Hydroxychloroquine sulfate	27 (19.0)
Immunosuppressants/immunomodulatory agents, n (%)	108 (76.1)
Azathioprine	17 (12.0)
Cyclosporin	14 (9.9)
Leflunomide	1 (0.7)
Methotrexate	22 (15.5)
Mizoribine	17 (12.0)
Mycophenolate mofetil	25 (17.6)
Pimecrolimus	2 (1.4)
Tacrolimus	38 (26.8)
Aspirin, n (%)	17 (12.0)
NSAIDs, n (%)	47 (33.1)

Baseline was defined as the last available value prior to belimumab initiation: Day 1 of the parent study for patients randomised to belimumab and Week 52 of the parent study for patients randomised to placebo.

*Patients may have been counted in more than one category.

†SLE flares reported between the last SLE flare assessment and 'baseline'.

‡ANA units were 'index' for patients from BEL113750 and 'titre' for patients from BEL112341.

§Or prednisone equivalent.

¶Two patients did not receive corticosteroids at baseline and therefore were counted as zero dose.

**One patient was counted in both hydroxychloroquine (with the start date of 2003 but no end date) and hydroxychloroquine sulfate (with the start date of 2013 and end date of 2016) categories and therefore, the two individual antimalarial categories include one extra patient compared with the overall antimalarials group.

ANA, antinuclear antibodies; BILAG, British Isles Lupus Assessment Group; BMI, body mass index; dsDNA, double-stranded DNA; NSAIDs, non-steroidal anti-inflammatory drugs; PGA, Physician Global Assessment; SD, standard deviation; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment-SLE Disease Activity Index; SLE, systemic lupus erythematosus.

the most frequently reported SAEs (reported in three patients each (2.1%); table 2). The highest SAE rate by system organ class was infections and infestations (6.4 events/100 patient-years) (table 3).

Overall, 57.0% (81/142) of patients experienced a treatment-emergent AE considered by the investigator to be at least possibly treatment related (table 2). Treatment-related AEs with >5% incidence at any time post first dose of belimumab were nasopharyngitis (15.5%) and herpes zoster (8.5%; data not shown).

In total, 4.9% (7/142) of patients experienced an AE leading to treatment discontinuation/study withdrawal (1.7 events/100 patient-years). One (0.7%) death was reported during the follow-up period due to endocarditis that began 55 days after the final belimumab dose (considered by the investigator to be unrelated to study treatment) (tables 2 and 3).

AESI rates per 100 patient-years are presented in table 3. One malignancy (angiocentric lymphoma) occurred in Year 1–2; the overall rate for malignancies at any time post first dose of belimumab was 0.2 events/100 patient-years.

Table 2 Overall summary of treatment-emergent AE* incidence by year interval (safety population; N=142)

	Number of patients (%)†							
	Any time post first dose of belimumab‡ (N=142)	Year 0–1 (n=142)	Year 1–2 (n=136)	Year 2–3 (n=108)	Year 3–4 (n=79)	Year 4–5 (n=32)	Year 5–6 (n=24)	Year 6+§ (n=13)
AE	139 (97.9)	133 (93.7)	122 (89.7)	81 (75.0)	59 (74.7)	30 (93.8)	24 (100.0)	9 (69.2)
AE preferred terms occurring in ≥10% of patients:								
Nasopharyngitis	86 (60.6)	49 (34.5)	60 (44.1)	33 (30.6)	22 (27.8)	16 (50.0)	7 (29.2)	3 (23.1)
Headache	40 (28.2)	22 (15.5)	15 (11.0)	9 (8.3)	6 (7.6)	4 (12.5)	3 (12.5)	0
Cough	26 (18.3)	14 (9.9)	9 (6.6)	6 (5.6)	4 (5.1)	3 (9.4)	1 (4.2)	0
Herpes zoster	26 (18.3)	10 (7.0)	10 (7.4)	2 (1.9)	2 (2.5)	1 (3.1)	0	0
Viral upper respiratory tract infection	26 (18.3)	11 (7.7)	14 (10.3)	4 (3.7)	1 (1.3)	0	0	0
Upper abdominal pain	23 (16.2)	13 (9.2)	3 (2.2)	4 (3.7)	4 (5.1)	2 (6.3)	0	0
Nausea	23 (16.2)	14 (9.9)	8 (5.9)	1 (0.9)	3 (3.8)	1 (3.1)	4 (16.7)	0
Diarrhoea	22 (15.5)	10 (7.0)	9 (6.6)	5 (4.6)	3 (3.8)	2 (6.3)	2 (8.3)	0
Upper respiratory tract infection	22 (15.5)	6 (4.2)	10 (7.4)	8 (7.4)	2 (2.5)	2 (6.3)	2 (8.3)	1 (7.7)
Fever	21 (14.8)	7 (4.9)	5 (3.7)	3 (2.8)	6 (7.6)	2 (6.3)	1 (4.2)	1 (7.7)
Influenza	20 (14.1)	6 (4.2)	2 (1.5)	5 (4.6)	6 (7.6)	1 (3.1)	2 (8.3)	1 (7.7)
Confusion	19 (13.4)	9 (6.3)	1 (0.7)	5 (4.6)	4 (5.1)	1 (3.1)	1 (4.2)	0
Gastroenteritis	19 (13.4)	7 (4.9)	3 (2.2)	2 (1.9)	4 (5.1)	2 (6.3)	0	1 (7.7)
Back pain	18 (12.7)	11 (7.7)	2 (1.5)	6 (5.6)	3 (3.8)	0	0	0
Abdominal pain	17 (12.0)	8 (5.6)	6 (4.4)	2 (1.9)	2 (2.5)	0	0	0
Constipation	17 (12.0)	8 (5.6)	4 (2.9)	1 (0.9)	2 (2.5)	0	4 (16.7)	1 (7.7)
Insomnia	17 (12.0)	7 (4.9)	3 (2.2)	3 (2.8)	1 (1.3)	1 (3.1)	2 (8.3)	1 (7.7)
Arthralgia	16 (11.3)	5 (3.5)	4 (2.9)	6 (5.6)	3 (3.8)	0	0	0
Myalgia	16 (11.3)	8 (5.6)	8 (5.9)	0	0	0	1 (4.2)	0
Vomiting	16 (11.3)	8 (5.6)	3 (2.2)	3 (2.8)	0	1 (3.1)	2 (8.3)	0
Treatment-related AE	81 (57.0)	46 (32.4)	38 (27.9)	20 (18.5)	11 (13.9)	9 (28.1)	3 (12.5)	1 (7.7)
SAE	48 (33.8)	24 (16.9)	18 (13.2)	9 (8.3)	6 (7.6)	2 (6.3)	3 (12.5)	0
Serious infections and infestations	24 (16.9)	14 (9.9)	5 (3.7)	2 (1.9)	3 (3.8)	0	1 (4.2)	0
SAE preferred terms occurring in ≥2 (1.0%) patients								
Cellulitis	3 (2.1)	0	0	1 (0.9)	1 (1.3)	0	1 (4.2)	0
Contusion	3 (2.1)	1 (0.7)	0	1 (0.9)	1 (1.3)	0	0	0
Herpes zoster	3 (2.1)	2 (1.4)	1 (0.7)	0	0	0	0	0
Endocarditis	2 (1.4)	0	1 (0.7)	0	0	0	0	0
Osteonecrosis	2 (1.4)	0	1 (0.7)	1 (0.9)	0	0	0	0
Pyelonephritis acute	2 (1.4)	2 (1.4)	0	0	0	0	0	0
Fever	2 (1.4)	0	2 (1.5)	0	0	0	0	0
Uterine leiomyoma	2 (1.4)	0	1 (0.7)	0	1 (1.3)	0	0	0
Severe AE¶	27 (19.0)	12 (8.5)	10 (7.4)	7 (6.5)	2 (2.5)	1 (3.1)	1 (4.2)	0

Continued

Table 2 Continued

	Number of patients (%)†							
	Any time post first dose of belimumab‡ (N=142)	Year 0–1 (n=142)	Year 1–2 (n=136)	Year 2–3 (n=108)	Year 3–4 (n=79)	Year 4–5 (n=32)	Year 5–6 (n=24)	Year 6+§ (n=13)
Severe AE preferred terms occurring in ≥2 (1.0%) patients								
Myalgia	3 (2.1)	1 (0.7)	2 (1.5)	0	0	0	0	0
Fever	2 (1.4)	1 (0.7)	1 (0.7)	0	0	0	0	0
AE resulting in study drug discontinuation	7 (4.9)	1 (0.7)	3 (2.2)	2 (1.9)	0	1 (3.1)	0	0
Deaths**	1 (0.7)	0	0	0	0	0	0	0

*Treatment-emergent AEs were defined as AEs that started on or after first dose of belimumab (see the Statistical analysis section).

†Each column shows number of patients who had ≥1 AE meeting the criterion for that year. Percentages were based on number of patients who started each year of treatment.

‡Post first belimumab dose (baseline) includes time on study up to the 16-week follow-up visit post last dose. Data from Year 0 to a patient's exit visit (4 weeks post last dose) are shown by years of study participation.

§Year 6+ represents Year 6–7 of belimumab treatment. No patients had exposure >7 years.

¶For severe AEs, events listed as life-threatening were included in the count.

**This event occurred during the 16-week follow-up period. The corresponding AE started after the exit visit, and therefore is counted only in the 'Any time post first dose of belimumab' column and not in any year interval.

AE, adverse event; SAE, serious AE.

There were no serious anaphylaxis/hypersensitivity reactions. One case of tuberculosis was reported during Year 2–3 (overall rate of 0.2 events/100 patient-years). One serious event of depression was reported (0.2 events/100 patient-years). There were no completed suicides or suicide attempts.

The annual incidence and rate of AEs of all categories, as well as AESI generally remained stable or declined throughout the study.

No trends of clinical concern were observed over time with regard to incidence of grade 3 or 4 values in haematology parameters, clinical chemistry and urinary values. There were no grade 3 or 4 serum IgG values reported post first dose of belimumab.

One patient from Japan tested positive for antidrug antibodies at the exit visit (4 weeks post last dose of belimumab), but they were confirmed as negative at the 16-week follow-up visit. This patient experienced maculopapular rash, cellulitis, thrombophlebitis and herpes zoster, which were considered by the investigator as unrelated to study treatment.

Efficacy results

Overall, the proportion of SRI4 responders during belimumab treatment increased from 47.8% (65/136) at Year 1, Week 24, to 68.2% (15/22) at Year 6, Week 48 (figure 3). Similarly, the proportion of patients with a ≥4-point reduction from baseline in SELENA-SLEDAI score increased from 51.5% (70/136) in Year 1, Week 24, to 77.3% (17/22) in Year 6, Week 48. The proportion of patients with no worsening in PGA (range of

91.3%–100.0%) and no new BILAG 1A/2B domain scores remained stable over time (range of 93.3%–100.0%).

Only 14.8% (21/142) of patients experienced ≥1 severe SFI flare post first dose of belimumab (24 severe flares; 5.2 events/100 patient-years). For patients who had a severe flare post first dose of belimumab, the median (IQR) time to first severe flare post first dose of belimumab was 585 (153.0, 882.0) days. Overall, 75.4% (107/142) of patients experienced any SFI flare post first dose of belimumab (75.8 events/100 patient-years) during belimumab treatment. The median (IQR) time to first SFI flare was 198 (89, 882) days. Only 25.4% (36/142) of patients experienced ≥1 new BILAG 1A/2B flare and 17.6% (25/142) had ≥1 new BILAG A flare post first dose of belimumab. A total of 30.3% (43/142) of patients experienced a renal flare post first dose of belimumab.

A total of 81 patients received a prednisone-equivalent dose >7.5 mg/day at baseline. The median (min, max) number of days any time post first dose of belimumab that the daily prednisone-equivalent dose was ≤7.5 mg/day or had been reduced by 50% from baseline was 584 (0, 2267). For these patients, the percentage receiving ≤7.5 mg/day prednisone dose at any visit from Year 1, Week 24, up to Year 6, Week 48, ranged from 22.2% (18/81) to 76.9% (10/13), respectively. For patients receiving ≤7.5 mg/day prednisone dose at baseline (n=61), the percentage receiving >7.5 mg/day prednisone dose at any visit from Year 1, Week 24, up to Year 6, Week 48, ranged from 8.2% (5/61) to 10.0% (1/10), respectively. For all patients, the median (IQR) per cent change from baseline in prednisone-equivalent dose decreased over time. At Year

Table 3 Event rates of treatment-emergent AEs by year interval (safety population, N=142)

	Number (rate) of events*									
	Any time post first dose of belimumab†	Year 0-1	Year 1-2	Year 2-3	Year 3-4	Year 4-5	Year 5-6	Year 6-7	Year 8-9	Year 10-11
	Patient-years=471	Patient-years=139	Patient-years=125	Patient-years=91	Patient-years=52	Patient-years=28	Patient-years=19	Patient-years=5		
AEs	2250 (477.2)	733 (526.0)	564 (452.9)	393 (429.8)	245 (472.9)	135 (483.5)	119 (623.9)	20 (417.6)		
Treatment-related AEs	262 (55.6)	99 (71.0)	94 (75.5)	33 (36.1)	13 (25.1)	15 (53.7)	6 (31.5)	1 (20.9)		
SAE	78 (16.5)	28 (20.1)	22 (17.7)	13 (14.2)	6 (11.6)	2 (7.2)	4 (21.0)	0		
Serious infections and infestations	30 (6.4)	14 (10.0)	8 (6.4)	2 (2.2)	3 (5.8)	0	2 (10.5)	0		
Severe AEs	50 (10.6)	17 (12.2)	14 (11.2)	10 (10.9)	2 (3.9)	1 (3.6)	2 (10.5)	0		
AEs resulting in study discontinuation	8 (1.7)	1 (0.7)	4 (3.2)	2 (2.2)	0	1 (3.6)	0	0		
AES†										
Malignant neoplasms§¶	1 (0.2)	0	1 (0.8)	0	0	0	0	0		
Any postinfusion systemic reactions**	26 (5.5)	10 (7.2)	4 (3.2)	4 (4.4)	2 (3.9)	5 (17.9)	1 (5.2)	0		
All infections of special interest§§††	37 (7.8)	13 (9.3)	12 (9.6)	4 (4.4)	2 (3.9)	1 (3.6)	1 (5.2)	0		
Serious	6 (1.3)	3 (2.2)	2 (1.6)	1 (1.1)	0	0	0	0		
All opportunistic infections‡‡	11 (2.3)	3 (2.2)	4 (3.2)	1 (1.1)	1 (1.9)	0	0	0		
Serious‡‡	0	0	0	0	0	0	0	0		
Active TB§	1 (0.2)	0	0	1 (1.1)	0	0	0	0		
Herpes zoster§§§	28 (5.9)	11 (7.9)	10 (8.0)	2 (2.2)	2 (3.9)	1 (3.6)	0	0		
Serious	4 (0.8)	3 (2.2)	1 (0.8)	0	0	0	0	0		
Recurrent opportunistic	6 (1.3)	2 (1.4)	3 (2.4)	0	0	0	0	0		
Disseminated opportunistic	5 (1.1)	0 (0.7)	1 (0.8)	1 (1.1)	1 (1.9)	0	0	0		
Sepsis§	4 (0.8)	0	0	1 (1.1)	0	0	1 (5.2)	0		
Depression§§	12 (2.5)	5 (3.6)	2 (1.6)	1 (1.1)	2 (3.9)	0	0	0		
Deaths***	1 (0.2)	0	0	0	0	0	0	0		

The corresponding AE started after the exit visit, and therefore is counted only in the 'Any time post first dose of belimumab' column and not in any year interval.
 *Each column shows the number of reported AEs for that year and the rate of events per 100 patient-years.
 †Post first belimumab dose (baseline) includes time on study up to the 16-week follow-up visit post last dose. Data from Year 0 to a patient's exit visit (4 weeks post last dose) are shown by years of study participation.
 ‡Year 6+ represents Year 6-7 of belimumab treatment. No patients had exposure >7 years.
 §Per Custom MedDRA query (V22.0).
 ¶No skin malignancies reported.
 **No serious postinfusion systemic reactions reported.
 ††All infections of special interest are limited to opportunistic infections, active TB, herpes zoster and sepsis.
 ‡‡Per sponsor adjudication.
 §§Not all herpes zoster events were recurrent or disseminated.
 †††Per MedDRA preferred term.
 ***This event occurred during the 16-week follow-up period. The corresponding AE started after the exit visit, and therefore is counted only in the 'Any time post first dose of belimumab' column and not in any year interval.
 AE, adverse event; AESI, AE of special interest; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious AE; TB, tuberculosis.

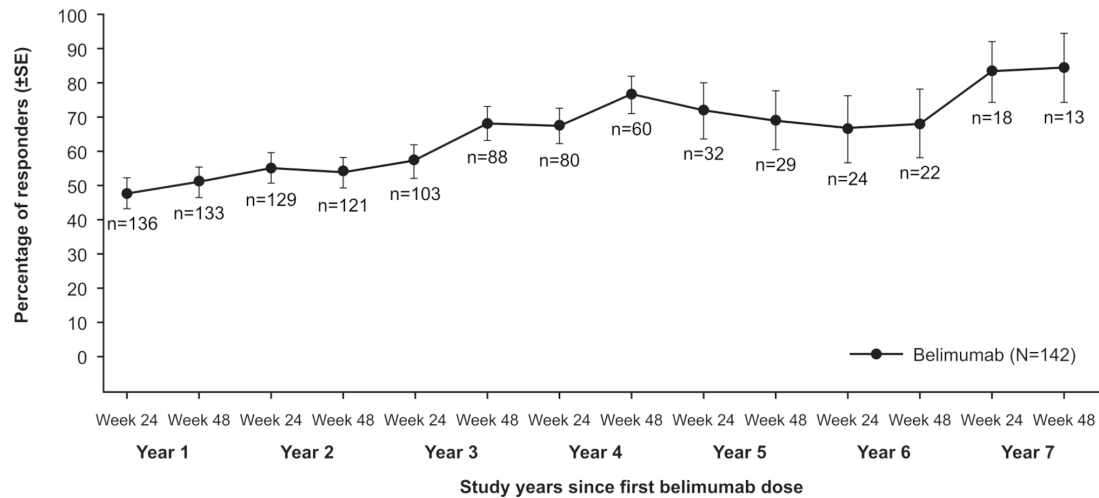


Figure 3 SRI4 response rate during belimumab treatment over time (safety population, N=142). Baseline was defined as the last available value prior to belimumab initiation: Day 1 of the parent study for patients randomised to belimumab and Week 52 of the parent study for patients randomised to placebo. SLE, systemic lupus erythematosus; SRI, SLE Responder Index.

3, Week 48 (n=90), the median (IQR) per cent change from baseline in prednisone-equivalent dose was -33.33 (-50.0, -6.7) and remained decreased through to study end.

Mean SELENA-SLEDAI Score and the mean PGA Score generally improved over time (online supplemental figure 1). There was little change in SDI Score from baseline. No more than four patients from BEL113750 and no more than two patients from BEL112341 had SDI worsening (change >0) compared with baseline at any Week 48 and Week 24 visit, respectively.

Biomarkers

The IgG median per cent change from baseline decreased only slightly over time (online supplemental figure 2A). The median anti-dsDNA per cent change from baseline also decreased (online supplemental figure 2B). The median per cent change in C3 and C4 levels increased and generally remained at a raised level above baseline during belimumab treatment (online supplemental figure 2C). The levels of B-cell subsets either decreased or remained stable throughout the study (online supplemental table 3).

DISCUSSION

The results of this long-term, open-label continuation study of patients with SLE from Japan and South Korea demonstrated high retention of patients, with 104/142 patients completing the study, which reflects the effectiveness and safety of intravenous belimumab as an add-on to standard therapy for up to 7 years. The safety profile observed is consistent with that seen in previous randomised controlled trials and other continuation studies of 7–13 years' duration.^{21 22 24–27 29} The incidence of treatment-emergent AEs, including AESIs, generally remained stable or declined over time, and the overall immunogenicity response rate was low. The 0.7%

incidence of mortality in the current study is similar to the 0.7%–1.5% incidence reported in the previous 7–8-year belimumab continuation studies.^{25 26 30}

In this long-term continuation study, the treatment benefits of belimumab in patients with SLE from Japan and South Korea were maintained over time (up to 7 years). Of the patients remaining in the study at Year 6, Week 48, over two-thirds were SRI4 responders.

Although some patients have received hydroxychloroquine, an antimalarial agent recommended for patients with SLE for minimising risk of flares, at the discretion of the investigators, the number of patients receiving it in this study was low as the study began before the hydroxychloroquine was approved in Japan.³¹ Nonetheless, the majority of patients did not experience severe flares, consistent with belimumab use as observed in other long-term continuation studies.^{25 27}

The results of this study suggest that belimumab allows for corticosteroid dose reduction, as is evident from the progressive decrease in median (IQR) percentage change from baseline in prednisone-equivalent dose over time. These findings support the results of BLISS-52 and BLISS-76 studies, in which belimumab therapy showed a reduction in prednisone dose compared with standard therapy alone.^{21 22}

These benefits were coupled with increasing improvements over time in anti-dsDNA, C3 and C4, which is consistent with the results from previous studies and with the mechanism of action of belimumab as an antibody that specifically targets and inhibits the activity of BLyS.^{21 22} Together these outcomes suggest that decreases in disease activity with belimumab were associated with limited new organ damage accrual.

Limitations of interpretation of the results include the small sample size, particularly at later study visits, and the absence of a placebo control group meant that treatment comparisons could not be made. However, the number

of Japanese and Korean patients enrolled in this open-label study (N=142) was proportionate to the number of Japanese and Korean patients randomised in the double-blind phase of the parent studies (BEL113750, N=160; BEL112341, N=30). The inclusion of a placebo comparator group in a long-term, 7-year study would not be feasible and would also be considered unethical. Additionally, as patients had to complete the parent studies, the sample of patients included in this continuation study was self-selected and potentially more likely to respond well to belimumab over time. Furthermore, the results of this study are based on observed data with no imputation analyses for withdrawal, which may also bias the findings. Patients randomised to placebo in the double-blind period of the parent studies had lower mean SELENA-SLEDAI and PGA scores at baseline than patients randomised to belimumab, which could be due to different baseline timepoints (baseline for the belimumab group was at the start of the double-blind parent study; baseline for the placebo group was at the start of open-label period). This phenomenon was observed also in a previous belimumab study of similar design.³² Placebo-treated patients had already completed the parent studies during which their standard therapy and care would have been optimised and their disease activity would have been likely to decrease. Despite these limitations, the results of this open-label continuation analysis are consistent with the known safety and efficacy profile of belimumab.^{21 22 24 25 27 33}

In conclusion, the safety results of this 7-year study of patients with SLE from Japan and South Korea are consistent with those observed in previous 7–13-year open-label continuation studies of belimumab added to standard therapy. Reductions in disease activity and corticosteroids dose, in addition to a low rate of new organ damage accrual, suggest that patients with SLE from Japan and South Korea achieve long-term benefits from belimumab treatment.

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Author note MC and RK were employees of GlaxoSmithKline at the time of the study.

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