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ORIGINAL ARTICLE

Efficacy and safety of intravenous belimumab in a subgroup of South Korean patients with systemic lupus erythematosus enrolled into a Phase 3, randomized, placebo-controlled trial in North East Asia

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Abstract

Aim: This post hoc analysis evaluated the efficacy and safety of intravenous belimumab 10 mg/kg in the South Korean subgroup of patients with systemic lupus erythematosus (SLE) enrolled in the North East Asia (NEA) study (GSK Study BEL113750; NCT01345253).

Methods: NEA was a double-blind, placebo-controlled, randomized Phase 3 trial. Patients with active, autoantibody-positive SLE were randomized 2:1 to belimumab or placebo plus standard therapy administered on Days 0, 14, and 28, and then every 28 days up to Week 48. The primary efficacy endpoint in this analysis was SLE Responder Index 4 (SRI-4) response rate at Week 52, defined as the proportion of

patients achieving a ≥4-point reduction in Safety of Estrogens in Lupus Erythematosus National Assessment-SLE Disease Activity Index (SELENA-SLEDAI) score, no worsening (<0.3 increase from baseline) in Physician Global Assessment, no new British Isles Lupus Assessment Group (BILAG) A domain and <2 new BILAG B domain scores.

Results: Among 100 South Korean patients enrolled in NEA, 54/66 (81.8%) belimumab- and 24/34 (70.6%) placebo-treated patients completed the double-blind phase. Significantly more belimumab- than placebo-treated patients achieved SRI-4 response at Week 52 ($n = 35/66$, 53.0% vs. $n = 8/34$, 23.5%; odds ratio [OR; 95% confidence interval (CI)]: 3.67 [1.45, 9.28]; $p = .0061$). The proportion of patients experiencing ≥1 adverse event was similar between groups (belimumab: $n = 60/66$, 90.9% vs. placebo: $n = 31/34$, 91.2%). No new safety signals emerged in this subgroup analysis.

Conclusion: Belimumab was efficacious for the treatment of SLE and well tolerated among the South Korean subgroup of patients from the NEA study.

KEYWORDS
belimumab, efficacy, safety, South Korea, systemic lupus erythematosus

1 | INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic, relapsing–remitting autoimmune disease with heterogeneous clinical manifestations affecting multiple organs.[1,2] SLE is characterized by elevated levels of B-lymphocyte stimulator (BLyS), which facilitates B-cell hyperactivity,[3–5] and circulating autoantibodies that deposit in tissues and induce a pathogenic inflammatory cascade.[1]

The prevalence of SLE is greater in Asian populations than Caucasian populations, and Asian patients with SLE are more likely to experience more frequent and severe clinical manifestations than Caucasian patients.[6] In South Korea, the 2015 prevalence rate of SLE was 35.45 per 100000 person-years,[7] with studies between 2005 and 2015 reporting a trend of increasing prevalence.[7,8] The mortality rate among patients with SLE is higher than that of the general population, and non-Caucasian patients with SLE, including Asian patients, have an increased risk of mortality compared with their Caucasian counterparts.[9]

SLE is conventionally managed with antimalarials, non-steroidal anti-inflammatory drugs, glucocorticoids, and immunosuppressants.[10–12] However, long-term use of glucocorticoids for the management of SLE has been identified as a primary cause of irreversible organ damage accrual,[12–14] with high-dose glucocorticoids further increasing the risk of organ damage.[15] As such, therapies that modify the course of disease by controlling disease activity and facilitate a reduction in glucocorticoid use limit damage accrual and reduce morbidity and mortality.[12,16] The European Alliance of Associations for Rheumatology (EULAR) recommends that glucocorticoid use should be withdrawn where possible or minimized to less than 7.5 mg/day (prednisone-equivalent) when withdrawal is not possible.[10] The Asia-Pacific League of Associations for Rheumatology (APLAR) in the 2021 SLE consensus also emphasizes the importance of minimizing glucocorticoid use in SLE management.[17]

Belimumab, a recombinant human IgG1λ monoclonal antibody that binds to soluble BLyS, antagonizing its activity,[5] is an approved biologic treatment for SLE in patients ≥5 years of age in over 75 countries worldwide.[18–22] The APLAR recommends that belimumab is considered for active SLE manifestations that are refractory to standard therapy.[17] The international approval of belimumab was supported by several Phase 3 trials demonstrating its efficacy, safety, and steroid-sparing potential,[23–25] including the North East Asia trial of patients from China, Japan, and South Korea.[26] Despite its approval in South Korea,[27] studies of belimumab's efficacy and safety in this population are limited,[28] and further analyses are warranted to investigate the effect of belimumab in addition to standard therapy for South Korean patients with SLE.

This subgroup analysis of South Korean adult patients with SLE from the North East Asia trial aims to evaluate belimumab's efficacy and safety in this population. Given the trend of increasing prevalence of SLE in South Korea[7,8] and the need for glucocorticoid-sparing and disease-modifying therapy options, investigations into biologics such as belimumab are timely and relevant to this specific population.

2 | MATERIALS AND METHODS

2.1 | Study design

This post hoc analysis used individual patient-level data from South Korean patients enrolled in the North East Asia trial, a Phase 3, multicenter, randomized, double-blind, placebo-controlled, 52-week trial (GSK Study BEL113750; NCT01345253) that investigated the efficacy and safety of intravenous (IV) belimumab 10 mg/kg plus standard therapy in adult patients with SLE, versus placebo plus standard therapy. The North East Asia trial was conducted at 49 centers across China, Japan, and South Korea between May 2011

and September 2015. Its primary findings for the overall population have been published,[26] as well as findings for a subgroup of patients from Japan[29] and open-label continuation studies in Japan, South Korea,[28] and China.[30]

Details on the North East Asia trial design, patient inclusion/exclusion criteria, randomization, and endpoints have been published previously.[26] Briefly, eligible patients were randomized 2:1 to receive either belimumab 10 mg/kg IV or placebo, in addition to standard therapy, on Days 0, 14, and 28, and then every 28 days up to Week 48. Final double-blind efficacy and safety assessments were conducted at Week 52. All patients in the North East Asia trial provided written informed consent; the study received institutional review board approval and was conducted in accordance with the Declaration of Helsinki.

2.2 | Patients

South Korean patients enrolled in the North East Asia trial were included in this subgroup analysis. Inclusion and exclusion criteria are reported in Table S1. Briefly, patients were 18 years or older, had a diagnosis of SLE in accordance with the American College of Rheumatology criteria, had clinically active disease (Safety of Estrogens in Lupus Erythematosus National Assessment – SLE Disease Activity Index [SELENA-SLEDAI] score ≥8) and a positive antinuclear antibody test result at screening, and were taking a stable SLE-treatment regimen for at least 30 days. The main exclusion criteria were active nephritis or central nervous system lupus, or having received B-cell–targeted therapy.[26]

2.3 | Endpoints and assessments

The primary efficacy endpoint was SLE Responder Index 4 (SRI-4) response rate at Week 52, defined as the proportion of patients achieving a ≥4-point reduction in SELENA-SLEDAI score, no worsening (<0.3 increase from baseline) in Physician Global Assessment (PGA), no new British Isles Lupus Assessment Group (BILAG) A domain score, and <2 new BILAG B domain scores versus baseline.

Secondary and other efficacy endpoints included SRI-4 component responses at Week 52; SRI-4 response rate and SRI-4 component responses at Week 52, stratified by baseline SELENA-SLEDAI score (≤9 vs. ≥10); SRI-4 response rate by visit over 52 weeks; and SRI-7 response rate at Week 52, defined as a ≥7-point reduction from baseline in SELENA-SLEDAI score, no worsening (<0.3 increase from baseline) in PGA, no new BILAG A domain score, and <2 new BILAG B domain scores versus baseline.

Further disease activity endpoints included time to first severe flare (as defined by the modified SLE Flare Index [SFI]), BILAG improvement by organ domain at Week 52 among patients with an A or B domain score at baseline, changes from baseline over 52 weeks in complement C3 and C4 levels among patients with low levels at baseline (low C3 levels defined as <0.9 g/L and low C4 levels defined as <0.1 g/L), and changes in anti-double-stranded DNA (dsDNA) levels from baseline over 52 weeks among patients who were anti-dsDNA positive at baseline (defined as ≥30 IU/mL). Glucocorticoid use was evaluated by assessing the number of days patients received ≤7.5 mg/day and/or a 50% reduced glucocorticoid dose (prednisone-equivalent) from baseline, among patients receiving >7.5 mg/day at baseline, and by the cumulative glucocorticoid dose over 52 weeks. Glucocorticoid tapering was permitted after Week 24 at the investigator's discretion for patients with improving disease activity for at least 4 weeks.

Adverse events (AEs), serious AEs (SAEs), and AEs of special interest (AESIs; including malignant neoplasms, post-infusion systemic reactions, all infections, depression/suicide/self-injury, and deaths) were evaluated throughout the study.

2.4 | Statistical analysis

Efficacy and safety endpoints were assessed in the South Korean subgroup of the overall modified intent-to-treat (mITT) population of the North East Asia trial, which comprised all randomized patients who received at least one dose of study treatment.

The primary endpoint, SRI-4 response rate at Week 52, was analyzed using a logistic regression model with only the treatment group as an independent variable. Similarly, SRI-7 response rates at Week 52, SRI-4 component responses at Week 52, and SRI-4 response and its components at Week 52 when stratified by baseline SELENA-SLEDAI score were analyzed by a logistic regression model with treatment group as the only independent variable. BILAG improvement by organ domain at Week 52 was analyzed by Fischer's exact test. Changes from baseline in complement C3 and C4 levels over 52 weeks (in patients with low levels at baseline) were assessed using an analysis of covariance (ANCOVA) with treatment group as the only independent variable analyzed, and changes from baseline in anti-dsDNA levels (in patients who were anti-dsDNA positive at baseline) over 52 weeks were analyzed by Wilcoxon test. Time to first severe flare over 52 weeks was analyzed using a Cox proportional hazards model without adjustment for additional independent variables. Difference between groups in the number of days of daily glucocorticoid dose (prednisone-equivalent) ≤7.5 mg/day and/or reduced glucocorticoid dose (prednisone-equivalent) by 50% from baseline over 52 weeks and difference between groups in cumulative glucocorticoid dose (prednisone-equivalent) over 52 weeks were both analyzed using a rank ANCOVA model with treatment group as the only independent variable.

3 | RESULTS

3.1 | Patient population

Of the 707 patients in the North East Asia trial, 100 (14.1%) were from South Korea (Figure S1). Among these patients, 54/66 (81.8%)

patients randomized to belimumab, and 24/34 (70.6%) patients randomized to placebo completed the double-blind phase. The most common reason for study withdrawal before Week 52 in the belimumab group was patient request ($n=6/66$, 9.1%), with patients citing personal reasons for withdrawal or withdrawing consent without further explanation. Adverse events were the most common reason for withdrawal in the placebo group ($n=5/34$, 14.7%).

Baseline demographics and disease characteristics reported for South Korean patients were consistent with those in the overall North East Asia trial (Table 1).[26] The mean (SD) age of patients was 32.1 (8.82) years, and 93.0% ($n=93$) of patients were female. In general, baseline demographics and disease characteristics were similar across the patient cohorts, with a few differences.

3.2 | Efficacy

3.2.1 | SRI-4 and its components

Significantly more patients in the belimumab group than in the placebo group met the primary efficacy endpoint, an SRI-4 response at Week 52 ($n=35/66$, 53.0% vs. $n=8/34$, 23.5%; odds ratio [OR; 95% confidence interval (CI)]: 3.67 [1.45, 9.28]; $p=.0061$) (Figure 1A).

In SRI-4 component analyses at Week 52, a significantly greater proportion of patients in the belimumab group than in the placebo group achieved a ≥4-point reduction in SELENA-SLEDAI ($n=37/66$, 56.1% vs. $n=9/34$, 26.5%; OR [95% CI]: 3.54 [1.44, 8.75]; $p=.0061$) (Figure 1B) and had no new BILAG 1A/2B ($n=52/66$, 78.8% vs. $n=20/34$, 58.8%; OR [95% CI]: 2.60 [1.05, 6.41]; $p=.0380$). Additionally, numerically more patients treated with belimumab had no worsening in PGA at Week 52 versus patients treated with placebo ($n=50/66$, 75.8% vs. $n=23/34$, 67.6%; OR [95% CI]: 1.49 [0.60, 3.72]; $p=.3882$; Figure 1B).

Patients who had a baseline SELENA-SLEDAI score ≥10 demonstrated significant improvement with belimumab versus placebo in SRI-4 response ($n=26/40$, 65.0% vs. $n=6/21$, 28.6% responders; OR [95% CI]: 4.64 [1.47, 14.64]; $p=.0088$) and ≥4-point reduction in SELENA-SLEDAI ($n=28/40$, 70.0% vs. $n=7/21$, 33.3% responders; OR [95% CI]: 4.67 [1.51, 14.47]; $p=.0076$). The remaining SRI-4 components also showed a numerically favorable response to belimumab versus placebo, but not to the level of statistical significance (Table S2). Similarly, there were numerically more belimumab-treated than placebo-treated patients with a baseline SELENA-SLEDAI score ≤9 who were SRI-4 responders at Week 52 and had favorable responses across the SRI-4 components, but not to the level of statistical significance (Table S2).

3.2.2 | Secondary and other endpoints

Numerically, there were more patients in the belimumab group ($n=15/51$, 29.4%) than the placebo group ($n=5/31$, 16.1%) with an SRI-7 response at Week 52 (OR [95% CI]: 2.17 [0.70, 6.71]; $p=.1802$).

Severe flares were experienced by numerically fewer belimumab-treated patients ($n=11/66$, 16.7%) than placebo-treated patients ($n=9/24$, 26.5%) over the study duration (hazard ratio [95% CI]: 0.61 [0.25, 1.48]; $p=.2784$) (Figure 2).

Among patients with BILAG-reported organ system involvement at baseline, numerically more belimumab-treated patients than placebo-treated patients achieved an improvement in BILAG score at Week 52 in most of the organ systems, with the greatest treatment differences between belimumab and placebo groups noted in the hematologic (belimumab: $n=11/23$, 47.8% vs. placebo: $n=1/9$, 11.1%; treatment difference: 36.7%; $p=.1032$), musculoskeletal (belimumab: $n=8/14$, 57.1% vs. placebo: $n=2/7$, 28.6%; treatment difference: 28.6%; $p=.3615$), and mucocutaneous (belimumab: $n=18/32$, 56.3% vs. placebo: $n=5/17$, 29.4%; treatment difference: 26.8%; $p=.1317$) domains (Figure 3). However, these results were not statistically significant and must be interpreted with caution given the small sample size.

In patients with low C3 and C4 levels at baseline, greater increases in C3 and C4 levels were observed in patients treated with belimumab compared with placebo at Week 52 (difference in C3 levels [95% CI]: 0.10 g/L [0.02, 0.19], $p=.0164$; difference in C4 levels: 0.042 g/L [0.01, 0.07], $p=.0127$) (Figure S2A,B). In addition, a numerically greater reduction in anti-dsDNA antibodies from baseline was observed in favor of belimumab versus placebo at Week 52 (median [min, max] change from baseline: −63.0 IU/mL [−4987, 218] vs. −34.0 [−1153, 1571]; $p=.0556$), in patients who had anti-dsDNA positive results at baseline (Figure S2C).

3.2.3 | Glucocorticoid use

For patients receiving >7.5 mg/day glucocorticoid dose (prednisone-equivalent) at baseline, belimumab-treated patients had a numerically greater median (min, max) number of days with their dose reduced to ≤7.5 mg/day and/or by 50% over 52 weeks compared with placebo-treated patients (113.0 [0, 351.0] days vs. 78 [0, 365.0] days; $P=.6308$). The proportion of patients achieving the greatest number of days with daily glucocorticoid dose (prednisone-equivalent) ≤7.5 mg and/or reduced by 50% favored belimumab (Figure 4). The median (min, max) cumulative glucocorticoid dose over the 52 weeks was 2777.5 (456.3, 15405.9) mg prednisone-equivalent with belimumab treatment compared with 3258.1 (1332.5, 26001.4) mg prednisone-equivalent with placebo ($P=.1088$).

3.3 | Safety

The most common AEs are reported in Table 2. A similar proportion of patients experienced at least one AE in the belimumab ($n=60/66$, 90.9%) and placebo ($n=31/34$, 91.2%) groups, and the most common AEs were headache and nasopharyngitis (belimumab: $n=14/66$, 21.2% vs. placebo: $n=8/34$, 23.5%, for both). Comparing the belimumab group with the placebo group, there was an increased

TABLE 1 Baseline demographic and clinical characteristics.

Characteristic	Placebo ($N=34$)	Belimumab 10 mg/kg IV ($N=66$)
Mean (SD) age, years	31.3 (9.1)	32.5 (8.7)
Female, *n* (%)	32 (94.1)	61 (92.4)
Mean (SD) SELENA-SLEDAI score	11.6 (3.9)	10.6 (4.2)
SELENA-SLEDAI category, *n* (%)		
≤9	13 (38.2)	26 (39.4)
≥10	21 (61.8)	40 (60.6)
BILAG organ involvement, *n* (%)		
At least 1A or 2B	22 (64.7)	32 (48.5)
At least 1A	5 (14.7)	6 (9.1)
At least 1B	28 (82.4)	55 (83.3)
No A or B	5 (14.7)	9 (13.6)
BILAG organ domain involvement by category[a], *n* (%)		
Mucocutaneous	17 (50.0)	32 (48.5)
Hematologic	9 (26.5)	23 (34.8)
Renal	8 (23.5)	16 (24.2)
Musculoskeletal	7 (20.6)	14 (21.2)
Vascular	10 (29.4)	13 (19.7)
General	5 (14.7)	5 (7.6)
Cardiovascular and respiratory	1 (2.9)	1 (1.5)
Mean (SD) PGA score	1.7 (0.5)	1.5 (0.6)
PGA category, *n* (%)		
0–1	3 (8.8)	11 (16.7)
>1–2.5	30 (88.2)	54 (81.8)
>2.5	1 (2.9)	1 (1.5)
Low C3 (<0.9 g/L), *n* (%)	28 (82.4)	59 (89.4)
Low C4 (<0.1 g/L), *n* (%)	17 (50.0)	27 (40.9)
Positive for anti-dsDNA (≥30 IU/mL), *n* (%)	34 (100)	59 (89.4)
SLE concomitant medications, *n* (%)		
Glucocorticoid dose (prednisone-equivalent)	34 (100.0)	64 (97.0)
≤7.5 mg/day	13 (38.2)	31 (47.0)
>7.5 mg/day	21 (61.8)	33 (50.0)
Mean dose (SD), mg/day	11.9 (6.7)	11.0 (7.9)
Antimalarials	25 (73.5)	54 (81.8)
Other immunosuppressant and immunomodulatory agents[b]	23 (67.6)	48 (72.7)
Mycophenolic acid	10 (29.4)	19 (28.8)
Azathioprine	6 (17.6)	16 (24.2)
Methotrexate	6 (17.6)	11 (16.7)
Cyclosporin	4 (11.8)	6 (9.1)

Abbreviations: BILAG, British Isles Lupus Assessment Group; C, complement; dsDNA, double-stranded DNA; IV, intravenous; PGA, Physician Global Assessment; SD, standard deviation; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment – SLE Disease Activity Index; SFI, SLE Flare Index; SLE, systemic lupus erythematosus.

[a]A and B domain scores only.

[b]Immunosuppressant and immunomodulatory agents received by >10% of patients in either group included in the table; additional agents were: mizoribine (belimumab, $n=1/66$ [1.5%]; placebo, $n=1/34$ [2.9%]), tacrolimus (belimumab, $n=1/66$ [1.5]; placebo $n=1/34$ [2.9]), and leflunomide (belimumab, $n=1/66$ [1.5%]; placebo, $n=0$).

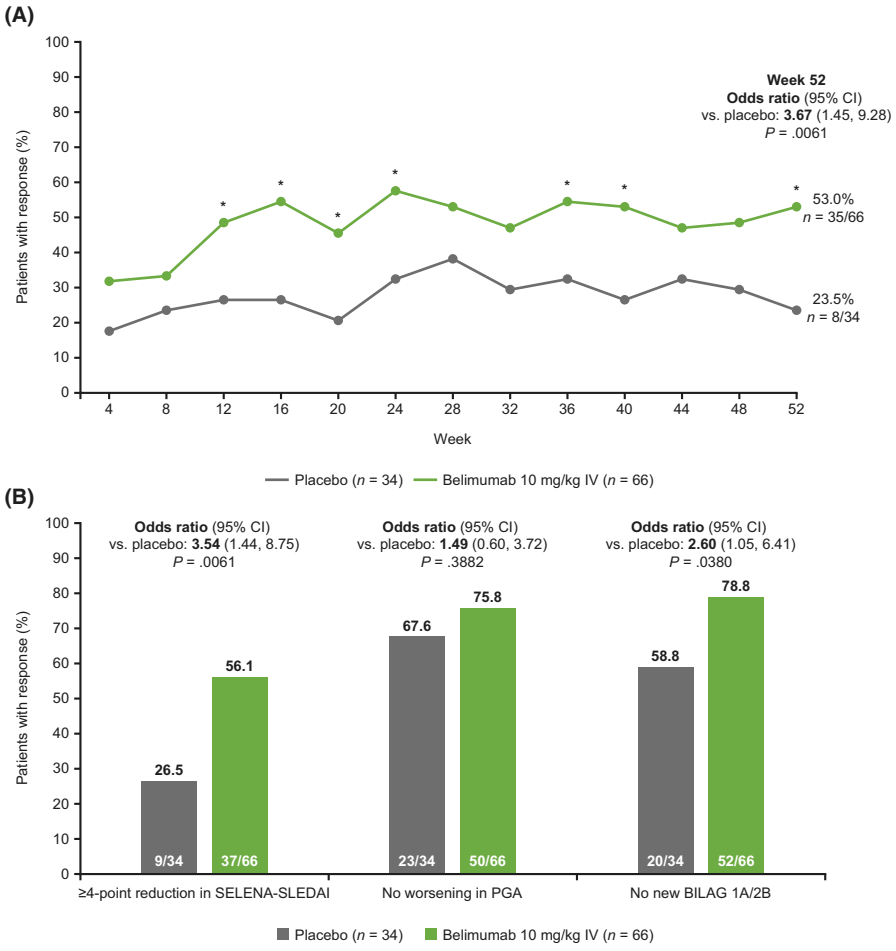


FIGURE 1 SRI-4 response rate by visit over 52 weeks (A) and SRI-4 components at Week 52 (B) ($N = 100$). *$p < .05$. BILAG, British Isles Lupus Assessment Group; CI, confidence interval; IV, intravenous; PGA, Physician Global Assessment; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment – Systemic Lupus Erythematosus Disease Activity Index; SRI-4, Systemic Lupus Erythematosus Responder Index 4.

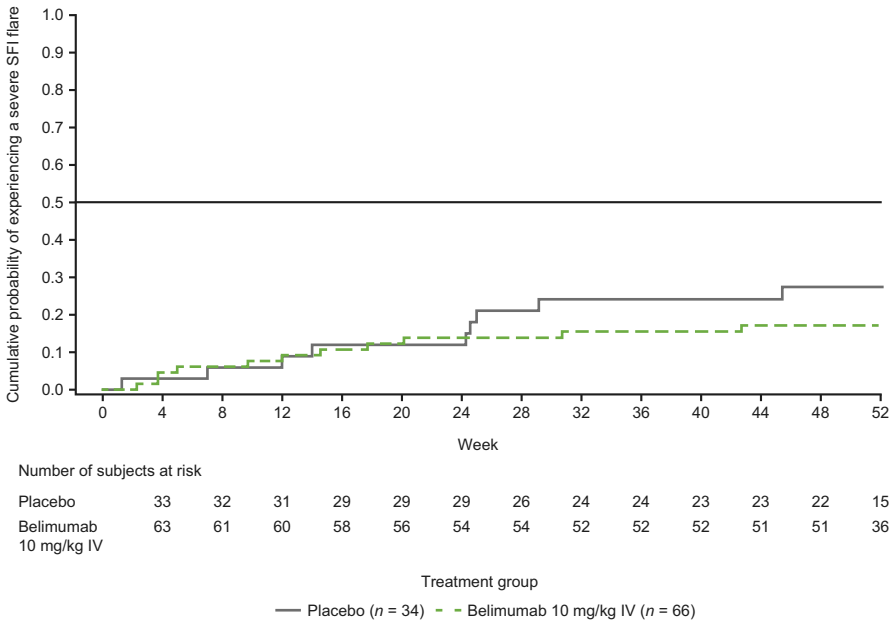


FIGURE 2 Time to first severe flare over 52 weeks ($N = 100$). IV, intravenous; SFI, systemic lupus erythematosus flare index.

incidence of viral upper respiratory tract infection (belimumab: $n = 10/66$, 15.2% vs. placebo: $n = 1/34$, 2.9%), cough (belimumab: $n = 15/66$, 22.7% vs. placebo: $n = 5/34$, 14.7%), nausea (belimumab: $n = 7/66$, 10.6% vs. placebo: $n = 2/34$ 5.9%), upper abdominal pain (belimumab: $n = 8/66$, 12.1% vs. placebo: $n = 3/34$, 8.8%), and diarrhea (belimumab: $n = 8/66$, 12.1% vs. placebo: $n = 4/34$, 11.8%) in the belimumab group. At least one SAE was experienced by 16/66 (24.2%) belimumab-treated and 11/34 (32.4%) placebo-treated patients. Similar incidences of AESIs were reported in the belimumab and placebo groups (Table 2), including post-infusion systemic reactions

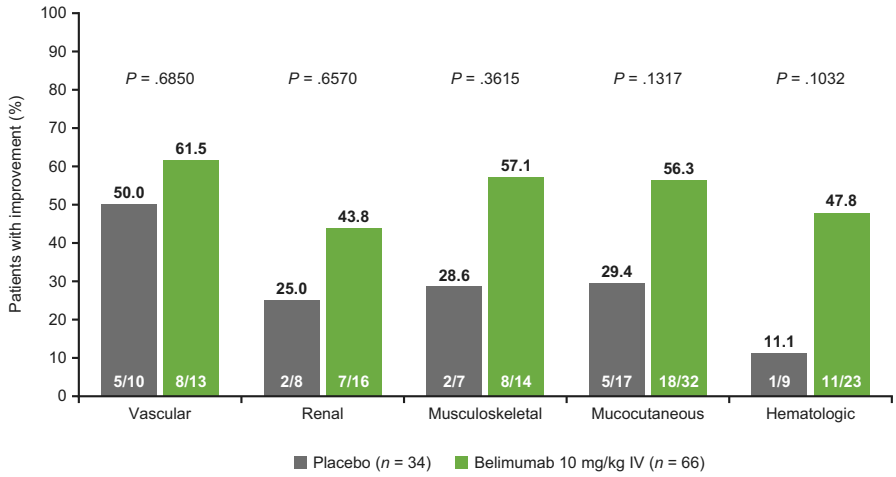
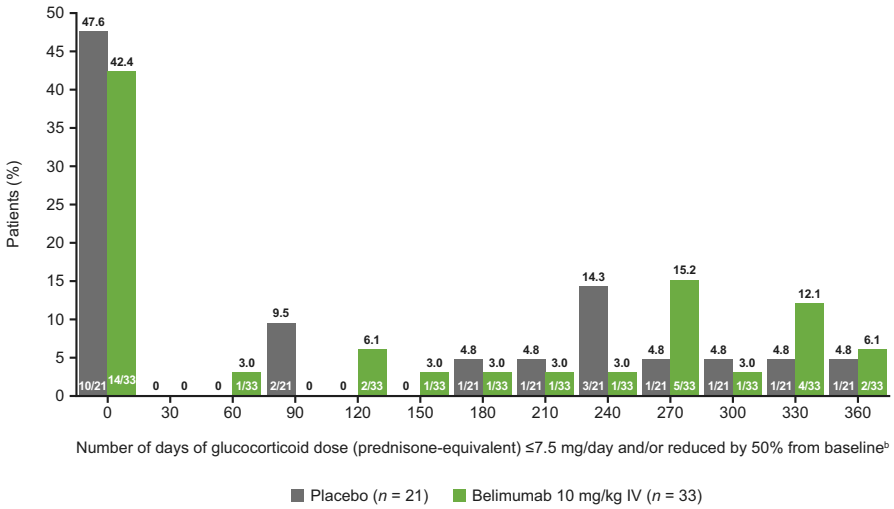


FIGURE 3 Patients with organ system improvement[a] by BILAG at Week 52, among patients with baseline involvement[b]. [a]Improvement was defined as changing from a score of A to B, C, or D, or changing from a score of B to C or D; [b]patients with A or B score at baseline. Improvements in BILAG domains general (belimumab $n=4/5$ vs. placebo $n=1/5$; $p=.2063$) and cardiovascular and respiratory (belimumab $n=1/1$ vs. placebo $n=1/1$; p value not calculable) not shown in figure due to low patient numbers with baseline involvement. BILAG, British Isles Lupus Assessment Group; IV, intravenous.

FIGURE 4 Proportion of patients with daily glucocorticoid dose (prednisone-equivalent) ≤7.5 mg and/or reduced by 50%[a] in each 30-day interval. [a]Among patients that had a baseline steroid dose >7.5 mg/day; [b]the number of days indicates the midpoint of the interval, that is, the proportion of patients at 30 days includes patients with daily glucocorticoid dose ≤7.5 mg and/or reduced by 50% for 15–44 days. IV, intravenous.



($n=22/66$, 33.3% vs. $n=12/34$, 35.3%); infections of special interest ($n=7/66$, 10.6% vs. $n=4/34$, 11.8%), such as herpes zoster ($n=4/66$, 6.1% vs. $n=2/34$, 5.9%) and tuberculosis ($n=0$ vs. $n=1/34$, 2.9%); and malignancies, including nonmelanoma skin cancer ($n=0$ for both groups). No belimumab-treated patient experienced leukopenia or lymphopenia ($n=0$ for both) versus 4/34 (11.8%) and 1/34 (2.9%) placebo-treated patients, respectively. One patient in the belimumab group had an AE of decreased lymphocyte count ($n=1/66$, 1.5%), with no cases in the placebo group ($n=0$). No belimumab-treated patients and 2/34 (5.9%) placebo-treated patients experienced depression/suicide/self-injury. No deaths were reported.

4 | DISCUSSION

This subgroup analysis furthered the work of the North East Asia trial in defining the role of belimumab treatment for North East Asian patients with SLE. Our analysis confirms the efficacy and safety of belimumab in South Korean patients with SLE, with findings consistent with belimumab trials performed in Asia[26,28] and internationally,[23–25] thus supporting belimumab 10 mg/kg IV plus standard therapy as an efficacious treatment option for patients with SLE from South Korea.

The primary efficacy endpoint, SRI-4 response at Week 52, was met by significantly more patients receiving belimumab than placebo, consistent with the findings of previous Phase 3 belimumab trials in SLE patients.[23–26] The higher number of SRI-4 responders in the belimumab group compared with the placebo group was driven by a greater proportion of patients achieving a response in each component of the SRI-4, with significantly more belimumab-treated patients experiencing a ≥4-point reduction in SELENA-SLEDAI and no new BILAG 1A/2B at Week 52 compared with placebo.

In this analysis, patients with higher disease activity (baseline SELENA-SLEDAI score of ≥10) achieved a significant SRI-4

TABLE 2 Most common adverse events and adverse events of special interest.

AEs, *n* (%)	Placebo (*N* = 34)	Belimumab 10 mg/kg IV (*N* = 66)
Any AE[a]	31 (91.2)	60 (90.9)
SAE	11 (32.4)	16 (24.2)
Most common AEs by preferred term (occurring in ≥10% of patients in either group)		
Headache	8 (23.5)	14 (21.2)
Nasopharyngitis	8 (23.5)	14 (21.2)
Cough	5 (14.7)	15 (22.7)
Pyrexia	9 (26.5)	7 (10.6)
Diarrhea	4 (11.8)	8 (12.1)
Abdominal pain	6 (17.6)	5 (7.6)
Abdominal pain upper	3 (8.8)	8 (12.1)
Viral upper respiratory tract infection	1 (2.9)	10 (15.2)
Nausea	2 (5.9)	7 (10.6)
Rhinorrhea	4 (11.8)	3 (4.5)
Leukopenia	4 (11.8)	0
AESIs (by category)		
Malignancies, including NMSC	0	0
Post-infusion systemic reactions (any event)	12 (35.3)	22 (33.3)
All infections of special interest	4 (11.8)	7 (10.6)
Serious infections	2 (5.9)	3 (4.5)
All opportunistic infections per GSK adjudication	1 (2.9)	3 (4.5)
Active tuberculosis	1 (2.9)	0
All herpes zoster	2 (5.9)	4 (6.1)
Depression/suicide/self-injury	2 (5.9)	0
Depression	2 (5.9)	0
Suicide/self-injury	1 (2.9)	0
Serious suicide/self-injury per GSK adjudication	1 (2.9)	0
Suicidal behavior per GSK adjudication	1 (2.9)	0
Deaths	0	0

Abbreviations: AE, adverse event; AESI, adverse event of special interest; IV, intravenous; NMSC, nonmelanoma skin cancer; SAE, serious AE.

[a]Patients counted only once per adverse event.

response and ≥4-point reduction in SELENA-SLEDAI at Week 52 with belimumab treatment compared with placebo, whereas for patients with lower disease activity (baseline SELENA-SLEDAI score of ≤9) there was a trend for higher treatment response in SRI-4 and its components with belimumab, but without statistical significance. The small number of patients with baseline SELENA-SLEDAI score of ≤9 (belimumab $n = 26$, placebo $n = 13$) likely contributed to the absence of significance. However, it has been reported elsewhere that belimumab's treatment effect is increased in patients with high disease activity versus low disease activity,[31,32] and this is especially important in the context of SLE treatment for Asian patients, who may have higher disease activity than non-Asian patients.[33]

A trend toward treatment effect consistent with the parent trial and other global Phase 3 trials was evident across many of the secondary endpoints in this South Korean subgroup analysis, including a reduction in steroid use[24–26] and risk of experiencing a severe flare.[23–26] These findings support belimumab's potential for reducing glucocorticoid usage in patients with SLE, a treatment goal that is in line with recent EULAR recommendations.[10] Additionally, belimumab was well tolerated in South Korean patients, with a smaller proportion of patients receiving belimumab withdrawing from the trial before Week 52 compared with placebo.

Incidence of AEs, SAEs, and AESIs was generally consistent with previous Phase 3 trials[23,24,26,28] and did not indicate any new safety concerns in this population. While there was a higher incidence of viral upper respiratory tract infection in the belimumab group compared with placebo (15.2% vs. 2.9%), the incidence with belimumab was generally similar to that reported previously for upper respiratory tract infections.[18,23,24,26,28] There was no notable difference in the incidence of any infection of special interest between treatment groups in this analysis, including tuberculosis and herpes zoster, opportunistic infections that are a concern for patients with SLE.[34] Additionally, there were no cases of leukopenia or lymphopenia reported in the belimumab group. There was a low incidence of depression/suicide/self-injury in the placebo group, with no AE of this class reported in the belimumab group.

4.1 | Limitations of current study

This South Korean subpopulation analysis was limited by the small number of South Korean patients included in the North East Asia trial ($n = 100$) and receiving belimumab ($n = 66$); as such, all results should be interpreted with caution. The North East Asia trial was not powered for subgroup analyses and therefore lacks sufficient statistical power to draw definitive conclusions. Patients with SLE with severe lupus kidney disease, active nephritis, or active central nervous system lupus were excluded from the North East Asia trial; therefore, belimumab could not be evaluated in these patients. However, considering the limited number of publications describing belimumab's efficacy and safety in South Korean patients with SLE, this analysis adds value to the existing literature.

Withdrawals were relatively high in the belimumab group (10.6%, due to patient's request or loss to follow-up) and in the placebo group (5.9%, due to patient's request only), which was likely due to the small sample size of the South Korean subgroup. In the overall North East Asia trial, the proportions of patients who withdrew

(by request or due to loss to follow-up) in the belimumab and placebo groups were 6.4% and 5.1%, respectively,[26] and in the pivotal Phase 3 belimumab trials, these proportions ranged from 0.7% to 10.2%.[23–25]

4.2 | Summary and conclusions

Consistent with previous clinical trials, belimumab was efficacious and well tolerated in South Korean adult patients with SLE, with no new safety concerns raised and a potential for steroid-sparing benefit. These findings support belimumab's role as an add-on therapy to standard treatment for SLE in South Korea.

AUTHOR CONTRIBUTIONS

All the authors involved in drafting or revising the article and approved of the submitted version. Data acquisition: C-HS, Y-WS, YMK, C-SC, WP, S-KK, S-GL, WTC, and S-CB. Data analysis and interpretation: C-HS, YL, S-BY, HQ, AANR, AH, Y-WS, YMK, C-SC, WP, S-KK, S-GL, WTC, and S-CB.

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CONFLICT OF INTEREST STATEMENT

YL, S-BY, HQ, AANR, and AH are employees of GSK. HQ and AH hold stocks and shares in GSK. C-HS has received payment for lectures, presentations, speakers' bureaus, manuscript writing, or educational events for AbbVie, Astellas, Janssen, JW Pharmaceutical, Samsung Bioepis, and Yuhan and worked as a paid consultant for GSK. Y-WS, YMK, C-SC, WP, S-KK, S-GL, WTC, and S-CB have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

Anonymized individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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