Safety of Belimumab in Adult Patients with Systemic Lupus Erythematosus: A Large Integrated Safety Analysis of Controlled Clinical Trial Data

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Daniel J Wallace[1], Tatsuya Atsumi[2], Mark Daniels[3], Anne Hammer[4], Paige Meizlik[5], Holly Quasny[6], Andreas Schwarting[7], Fengchun Zhang[8], David A Roth[9]

[1]Cedars-Sinai, Division of Rheumatology, Los Angeles, CA, USA; [2]Hokkaido University Hospital, Department of Rheumatology, Sapporo, Japan; [3]GlaxoSmithKline, Clinical Science Lupus, Collegeville, PA, USA; [4]GlaxoSmithKline, Biostatistics, Collegeville, PA, USA; [5]GlaxoSmithKline, Global Safety, Collegeville, PA, USA; [6]GlaxoSmithKline, Global Medical Affairs, Chapel Hill, NC, USA; [7]University Medical Center, Division of Rheumatology and Clinical Immunology, Mainz, Germany; [8]Peking Union Medical College Hospital, Internal Medicine Department, Beijing, China; [9]GlaxoSmithKline, Research and Development, Collegeville, PA, USA

Introduction

- SLE is a chronic autoimmune disorder associated with a variety of manifestations that can potentially lead to multiorgan failure and death[1,2]
- Long-term treatment goals for SLE include patient survival, prevention of organ damage and improvement of health-related quality of life[2]
- In 2011, BEL became the first biological drug approved for the treatment of SLE[3,4]
- BEL is a targeted human monoclonal antibody that binds and inhibits soluble human BLyS[3-5]
- BEL has demonstrated consistent efficacy in reducing disease activity and may reduce progression of damage[6-8]
- BEL is indicated in more than 70 countries for the treatment of patients with active, autoantibody-positive SLE who are receiving standard therapy[4,9-11]
- Safety data accrued from several individual randomised trials since its approval suggest BEL is generally well tolerated.[12-15] Integration of these data provides an additional opportunity to explore the safety of BEL

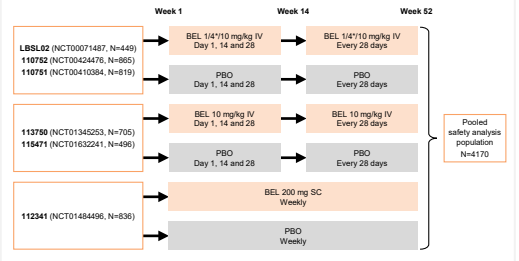
Objective

- To perform a pooled analysis of clinical studies to evaluate the safety of BEL in adults with SLE

Methods

- This was a pooled aggregated analysis of safety data from six randomised, placebo-controlled Phase 2 and Phase 3 BEL trials in patients with auto-antibody positive SLE ≥18 years of age (**Figure 1**).[6,7,12,13,16] Patients who received ≥1 dose of either BEL or PBO were included
- Safety analyses included incidence of AEs, SAEs, AESI and death in patients receiving BEL (all doses/formulations combined) versus PBO at Week 52

Figure 1. Overview of the 52-week studies included in the pooled safety analysis population



*4 mg/kg for Study LBSL02 only. Five Phase 3 trials and one Phase 2 trial (LBSL02) were included

Results

Patient characteristics

- Baseline demographics, disease characteristics and duration of treatment exposure were similar between treatment groups (**Table 1**)

Table 1. Baseline demographics and disease characteristics of the pooled safety analysis population

	BEL (IV + SC) N=2815	PBO (IV + SC) N=1355
Female, n (%)	2661 (94.5)	1268 (93.6)
Age (years), mean (SD)	37.5 (11.5)	37.8 (12.0)
Age category (years), n (%)		
≤45	2098 (74.5)	1011 (74.6)
>46 to <65	681 (24.2)	317 (23.4)
≥65	36 (1.3)	27 (2.0)
Race, n (%)*		
White	1100 (39.1)	516 (38.1)
Asian	836 (29.7)	418 (30.8)
Black African Ancestry	568 (20.2)	269 (19.9)
American Indian or Alaskan Native	307 (10.9)	149 (11.0)
Multiracial	26 (0.9)	15 (1.1)
Hispanic or Latino, n (%)	765 (27.2)	373 (27.5)
SLE duration (years), mean (SD)	6.7 (6.58)	6.8 (6.61)
SELENA-SLEDAI category, n (%)		
≤9	1315 (46.7)	612 (45.2)
≥10	1500 (53.3)	743 (54.8)
SELENA-SLEDAI score, mean (SD)	9.9 (3.7)	10.0 (3.8)
SLICC/ACR damage index score, n	2476	1242
Mean (SD)	0.6 (1.1)	0.6 (1.1)
Complement levels†, n (%)		
Low	1587 (56.4)	750 (55.4)
Not low	1228 (43.6)	605 (44.6)
Anti-ds DNA binding‡, n (%)		
High	1932 (68.6)	920 (67.9)
Not high	883 (31.4)	435 (32.1)
Study drug exposure duration (days)		
Mean (SD)	334.1 (92.6)	325.3 (97.4)
Median (IQR)	364 (361.0–372.0)	364 (357.0–371.0)

*Patients who checked >1 race category are counted under the individual category as well as the multiracial category; †Low = C3 or C4 values below the lower limit of normal; ‡High = anti-dsDNA ≥30 IU/mL

Patient disposition

- The pooled safety analysis population included 4170 patients (BEL: 2815, PBO: 1355)
- Overall, 81.0% (n=2280) of patients receiving BEL and 76.6% (n=1038) receiving PBO completed their Week-52 visit
- The most common reason for withdrawal in both groups was occurrence of an AE (BEL: n=169, 6.0%; PBO: n=97, 7.2%)

Adverse events

- Incidence of AEs, SAEs and death was similar across treatment groups (**Figure 2**)
- The most commonly reported SAEs by SOC in both groups were infections and infestations (BEL: 5.4%, PBO: 5.9%), renal and urinary disorders (BEL: 1.7%, PBO: 2.2%), and musculoskeletal and connective tissue disorders (BEL: 1.7%, PBO: 2.1%) (**Table 2**)

Figure 2. Summary of AEs, SAEs and death in the pooled safety analysis population by treatment group

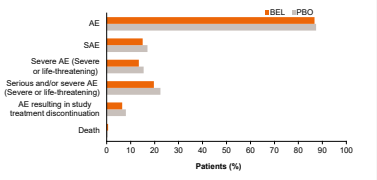


Table 2. Most common SAEs (experienced by ≥1% patients) by SOC in the pooled safety analysis population by treatment group

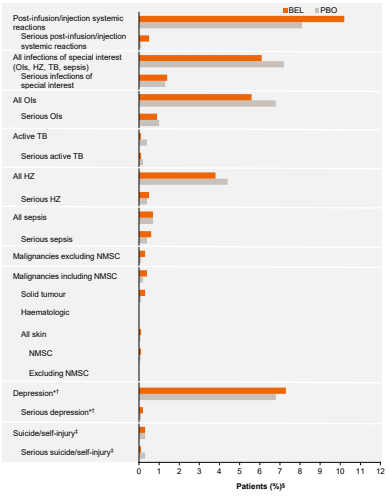
Variable, n (%)*	BEL (IV + SC) N=2815	PBO (IV + SC) N=1355
Any SAE	421 (15.0)	230 (17.0)
Infections and infestations	151 (5.4)	80 (5.9)
Renal and urinary disorders	48 (1.7)	30 (2.2)
Musculoskeletal and connective tissue disorders	48 (1.7)	28 (2.1)
Gastrointestinal disorders	45 (1.6)	26 (1.9)
Nervous system disorders	42 (1.5)	19 (1.4)
General disorders and administration site conditions	34 (1.2)	23 (1.7)
Respiratory, thoracic and mediastinal disorders	30 (1.1)	19 (1.4)
Injury, poisoning and procedural complications	31 (1.1)	13 (1.0)
Cardiac disorders	28 (1.0)	20 (1.5)
Vascular disorders	29 (1.0)	16 (1.2)
Blood and lymphatic system disorders	21 (0.7)	15 (1.1)

*Patients only counted once per category

Adverse events of special interest

- A greater proportion of patients experienced AESI with BEL compared with PBO for post-infusion/injection systemic reactions and depression/ suicide/self-injury (**Figure 3**)
- The proportion of patients experiencing infections, including HZ, and malignancy AESIs, was similar between groups (**Figure 3**)

Figure 3. Summary of AESIs in the pooled safety analysis population by treatment group



*Including mood disorders and anxiety; †Per custom MedDRA query; ‡Per standard MedDRA query; §Patients only counted once per category

Conclusions

- No unexpected safety findings were observed throughout all trials; however, more patients experienced depression (including mood disorders and anxiety) with BEL versus PBO
- The BEL safety profile was similar to that of PBO, and results from the pooled safety analyses were consistent with those observed for the individual studies
- These results continue to support a positive benefit–risk profile of BEL in the treatment of adults with SLE

Abbreviations

ACR, American College of Rheumatology; AE, adverse event; AESI, AE of special interest; BEL, belimumab; BLyS, B-lymphocyte stimulator; dsDNA, double-stranded DNA; HZ, herpes zoster; IQR, interquartile range; IV, intravenous; MedDRA, Medical Dictionary for Regulatory Activities; NMSC, non-melanoma skin cancer; OI, opportunistic infection; PBO, placebo; SAE, serious AE; SC, subcutaneous; SD, standard deviation; SLE, systemic lupus erythematosus; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment - Systemic Lupus Erythematosus Disease Activity Index; SLICC, Systemic Lupus International Collaborating Clinics; SOC, system organ class; TB, tuberculosis.

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Disclosures

DJW has worked as a consultant and has been a paid speaker for GSK. **TA** has received financial grants from GSK, and has been a consultant and a paid speaker for GSK. **MD, AH, PM, HQ** and **DAR** are employees of GSK and hold stocks and shares in the company. **AS** has received financial grants from GSK, AbbVie, Actelion, Novartis and Pfizer, has been a paid consultant for GSK, and has been a paid speaker for GSK, Amgen, Novartis, Pfizer and Roche. **FZ** has no disclosures to declare.

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Author email address: danielwallac@gmail.com

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