Paper

Safety of belimumab in adult patients with systemic lupus erythematosus: Results of a large integrated analysis of controlled clinical trial data

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

Abstract

Objectives: Systemic lupus erythematosus (SLE) is a chronic, autoimmune disease that affects multiple organ systems. Belimumab, a targeted human monoclonal antibody, binds to and inhibits soluble B-lymphocyte stimulator. The safety and efficacy of belimumab has consistently been demonstrated in multiple clinical trials for the treatment of patients with active SLE. Integration of these data provides an additional opportunity to explore the safety of belimumab in a larger and more diverse population. This post hoc pooled analysis of clinical studies evaluated the safety profile of belimumab versus placebo in adults with SLE.

Methods: This was a pooled post hoc analysis of 52-week safety data from one Phase 2 and five Phase 3 belimumab trials in adult patients with SLE. Patients received ≥1 dose of placebo or belimumab (1, 4, or 10 mg/kg intravenous or 200 mg subcutaneous), plus standard therapy. Outcomes included the incidence of adverse events (AEs), serious AEs (SAEs), severe AEs, AEs of special interest (AESI), and mortality.

Results: Across 4170 patients (placebo: N = 1355; belimumab: N = 2815), baseline demographics, disease characteristics, and treatment exposure were similar for placebo and belimumab. Most patients (placebo: 76.6%; belimumab: 81.0%) completed the protocol Week 52 visit. Overall, incidence of AEs, SAEs, severe AEs, AESI, and mortality were similar between groups. In both groups, the most commonly reported SAEs by system organ class were infections and infestations (placebo: 5.9%; belimumab: 5.4%) and renal and urinary disorders (placebo: 2.2%; belimumab: 1.7%). Additionally, a greater proportion of patients experienced AESI with belimumab versus placebo for post-infusion/injection systemic reactions (placebo: 8.1%; belimumab: 10.2%). Mortality rates were similar between groups (placebo: 0.4%; belimumab: 0.6%).

Conclusions: These results are consistent with those of the individual studies, BASE, BLISS-LN, and long-term extension studies, making belimumab one of the most studied SLE treatments for safety. Collectively, this evidence continues to support a positive benefit–risk profile of belimumab in the treatment of adult patients with SLE.

Keywords

autoimmune diseases, belimumab, biological products, safety, systemic lupus erythematosus

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

Corresponding author:
Holly Quasny, Research and Development, GSK, 410 Blackwell St, Durham, NC 27701, USA.
Email: holly.a.quasny@gsk.com

Introduction

Systemic lupus erythematosus (SLE) is a chronic, autoimmune disease that may affect multiple organ systems.[1] Treatment of patients with SLE is informed by type and intensity of clinical manifestations, organ involvement, and related disease severity.[1] For constitutional symptoms and mild-to-moderate SLE, recommended standard therapies (ST) include antimalarials, corticosteroids (CS), and non-steroidal anti-inflammatory drugs.[1,2] Immunosuppressants, calcineurin inhibitors, high-dose (pulse) CS, and belimumab (a biologic) are also recommended for patients with moderate-to-severe disease.[1–3] While STs improve disease control, there are safety concerns associated with such treatments, including CS-associated adverse events (AEs) and organ damage, and gonadotoxic effects of high-dose cyclophosphamide.[1,4] Other risks associated with immunosuppressants include malignancy and infections.[1,5] Therefore, there remains a need for safer and more effective SLE treatments.

Belimumab, a recombinant, human immunoglobin G1λ monoclonal antibody, binds and inhibits the biological activity of soluble B-lymphocyte stimulator protein and subsequently reduces B-cell survival.[6,7] Belimumab has been approved in several countries for the treatment of patients ≥5 years of age with active, autoantibody-positive SLE, and adult patients with lupus nephritis (LN) who are receiving ST.[8–11] A number of clinical trials have demonstrated the consistent safety and efficacy of belimumab in conjunction with ST in patients with SLE.[12–15] Additional safety data accrued from several randomized trials in specific patient populations further suggest that it is generally well tolerated.[15,16] The BLISS-NEA Phase 3 randomized clinical trial demonstrated the safety and efficacy of belimumab in Northeast Asian patients with SLE, reporting a similar incidence of AEs and AEs of special interest (AESI) for placebo and belimumab.[15] The overall incidence of serious AEs (SAEs) was greater for placebo than belimumab, and the most common AE in both groups was upper respiratory tract infection.[15] In the Phase 3/4 EMBRACE trial performed in patients of Black African ancestry, the incidence of AEs and AESI were similar in placebo and belimumab, and in line with the safety profiles of previous Phase 3 studies,[12–14] although the study did not meet the primary efficacy endpoint.[16] The integration of data from several randomized controlled trials therefore provides an additional opportunity to further explore the safety of belimumab in a larger and more diverse dataset. To this end, this pooled, post hoc analysis of six clinical trials evaluated the safety of belimumab in adults with SLE.

Methods

Study design and participants

This was a post hoc, pooled, integrated analysis of 52-week safety data from six randomized, placebo-controlled, Phase 2 (LBSL02 [NCT00071487][17]) or Phase 3 (BLISS-52 [NCT00424476],[13] BLISS-76 [NCT00410384],[12] BLISS-NEA [NCT01345253],[15] EMBRACE [Phase 3/4; NCT01632241],[16] and BLISS-SC [NCT01484496][14]) belimumab trials in adult patients with autoantibody-positive SLE (Figure 1). The methodologies and details of full study populations of these trials have been published previously.[12–17] The BLISS-LN (NCT01639339) Phase 3 clinical trial was not included in this analysis due to differences in the population (inclusion of patients with LN) and in the study design (cyclophosphamide [500 mg every 2 weeks for 6 infusions] or mycophenolate mofetil [3 g/day target] treatment at induction and a 2-year study duration).[18] The Belimumab Assessment of Safety in SLE (BASE; NCT01705977) Phase 4 clinical trial was also not included in this analysis due to differences in study size, population, and data collection.[19]

Eligibility criteria were similar across the pooled studies. Briefly, patients included in the six studies were aged ≥18 years with a diagnosis of SLE according to American College of Rheumatology (ACR) revised classification criteria,[20] had clinically active disease (defined as a Safety of Estrogens in Lupus Erythematosus National Assessment version of the SLE Disease Activity Index [SELENA-SLEDAI] score ≥4, 6, or 8, depending on the study) at screening, as well as seropositivity (antinuclear antibody titer ≥1:80 and/or anti–double-stranded DNA antibody level ≥30 IU/mL; for study LBSL02 no threshold was set at screening but a history of measurable autoantibodies was required) and a stable treatment regimen at screening or for ≥30 or ≥60 days (before the first study dose), depending on the study. Geographical regions of all enrollments were from Europe, North America, South America, South Africa, Middle East, Australia, and Asia. Patients were of diverse race and ethnicities, including White, Black African ancestry, Asian (East Asian, Southeast Asian, Central/South Asian, or Japanese heritage, Asian heritage unknown or mixed Asian race), and Hispanic or Latino.

All trials were conducted in accordance with the ethical principles of the Declaration of Helsinki, International Council for Harmonisation on Good Clinical Practice, and the applicable country-specific regulatory requirements. As reported in the primary publications, all trials were approved by local or central institutional review boards or ethics committees, and all patients provided written informed consent.[12–17]

Randomization and masking

In each study, patients were randomized and received treatment with either belimumab (intravenous [IV] or subcutaneous [SC]) or placebo, both in combination with ST.[12–17] All patients and study site personnel were blinded to trial agent assignment. Depending on the study, patients
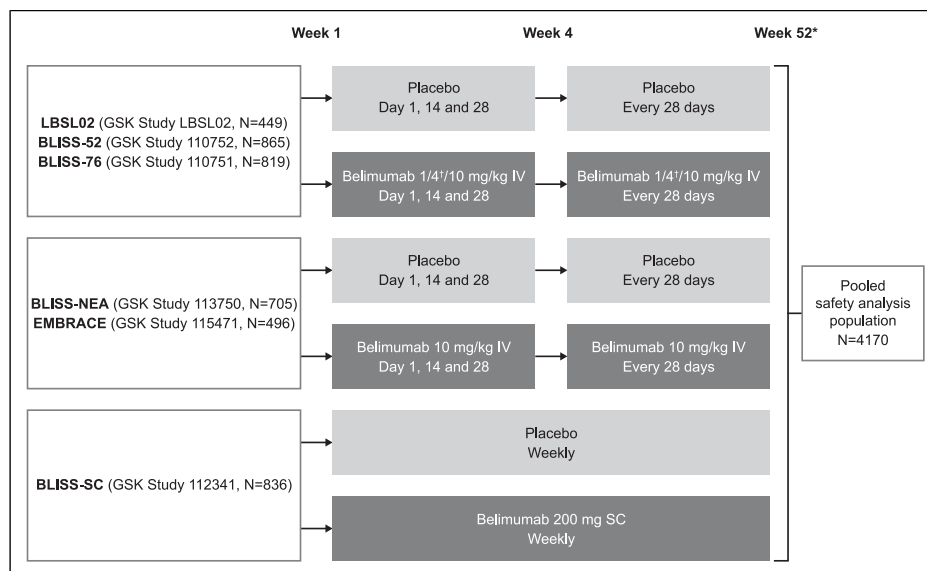
Figure 1. Overview of the studies included in the pooled safety analysis population.[12–17]
*The current analysis used Week 52 safety data from all studies. However, the treatment period of BLISS-76 was 72 weeks. [†]4 mg/kg for Study LBSL02 only. Five Phase 3 trials and one Phase 2 trial (LBSL02) were included. IV: intravenous; SC: subcutaneous.

were stratified at randomization by screening SELENA-SLEDAI score, proteinuria, country, region, race, ethnicity, or complement level.

Procedures

Patients within the six trials received either belimumab (1, 4, 10 mg/kg IV or 200 mg SC) or placebo in addition to ST[12–17] Patients enrolled in BLISS-52 and BLISS-76 received either placebo, or belimumab 1 or 10 mg/kg IV plus ST on Days 1, 14, 28, and every 28 days thereafter.[12,13] In Study LBSL02, patients with SLE received placebo or belimumab 1, 4, or 10 mg/kg IV plus ST on Days 1, 14, 28, and every 28 days thereafter.[17] In EMBRACE and BLISS-NEA, patients received placebo or belimumab 10 mg/kg IV plus ST on Days 1, 14, 28, and every 28 days thereafter.[15,16] Patients in BLISS-SC received placebo or belimumab 200 mg SC plus ST weekly.[14]

Outcomes

This pooled analysis evaluated the safety of belimumab (all doses and both formulations combined) versus placebo, both in combination with ST Safety outcomes included incidence of AEs, SAEs, severe (or life-threatening) AEs, AESI, and mortality in patients receiving belimumab (all doses and formulations combined) versus placebo at Week 52. All AEs were re-coded by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.0 during study integration. The MedDRA is an extensive and highly specific standardized medical terminology to allow sharing of regulatory information

internationally for medical products. A treatment-related AE was defined as an AE considered by the investigator to be potentially related to the study treatment.

Statistical analysis

The pooled safety analysis population was defined as all randomized patients who received ≥1 dose of study drug (planned treatment group; according to the dosing schedule outline in Figure 1) in the included studies. All safety analyses were descriptive only, as originally described in the reporting and analysis plan for each individual study. CS use was converted to prednisone-equivalent dose (mg/day).

Role of the funding source

The funder of the study contributed to its design, and participated in the collection, analysis, and interpretation of the data and in the writing, reviewing, and approval of the manuscript.

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of our research.

Results

Patient disposition

A total of 4170 patients (placebo: N = 1355; belimumab: N = 2815) were included in the pooled safety analysis

population. In total, 76.6% (n = 1038/1355) of patients receiving placebo and 81.0% (n = 2280/2815) of patients receiving belimumab completed their Week 52 visit (Table 1). The most common reason for trial withdrawal in both groups was occurrence of an AE (placebo: 7.2% [n = 97/1355]; belimumab: 6.0% [n = 169/2815]).

Baseline demographics, disease characteristics, and medication usage

Overall baseline demographics, disease characteristics, and duration of treatment exposure were similar between treatment groups (Table 2). Most patients were female (placebo: 93.6% [n = 1268/1355]; belimumab: 94.5% [n = 2661/2815]), with a mean age of 37.8 years in the placebo group and 37.5 years in the belimumab group. The most common race was White (placebo: 38.1% [n = 516/1355]; belimumab: 39.1% [n = 1100/2815]), Asian (placebo: 30.8% [n = 418/1355]; belimumab: 29.7% [n = 836/2815]) and Black African ancestry (placebo: 19.9% [n = 269/1355]; belimumab: 20.2% [n = 568/2815]). The majority of patients in both treatment groups had a SELENA-SLEDAI score ≥10 at baseline, with a mean SLE disease duration of 6.8 years in the placebo group and 6.7 years in the belimumab group. Both treatment groups had a mean SLICC/ACR damage index (SDI) score of 0.6 at baseline.

Mean baseline study drug exposure duration was similar for both treatment groups (Table 2). At baseline, most patients were receiving CS (placebo: 87.4% [n = 1184/1355]; belimumab: 85.4% [n = 2404/2815]) and/or anti-malarials (placebo: 70.6% [n = 956/1355]; belimumab: 68.7% [n = 1934/2815]; Table 2). Most patients were receiving a mean daily prednisone-equivalent dose >7.5 mg/day (placebo: 61.5% [n = 833/1355]; belimumab: 59.9%

[n = 1685/2815]), with a mean (standard deviation, SD) average daily prednisone dose of 12.0 (9.7) mg/day in the placebo group and 11.4 (9.6) mg/day in the belimumab group (Table 2). Approximately half of the patients were receiving immunosuppressants as part of ST (placebo: 52.5% [n = 712/1355]; belimumab: 51.3% [n = 1443/2815]).

Adverse events

The overall incidence of AEs was similar in the placebo and belimumab groups (87.4% [n = 1184/1355] and 86.7% [n = 2440/2815], respectively; Figure 2). A similar proportion of patients experienced AEs considered related to the study drug in the placebo and belimumab groups (placebo: 34.2% [n = 463/1355]; belimumab: 36.2% [n = 1019/2815]).

The proportion of patients who experienced ≥1 SAE was 17.0% (n = 230/1355) in the placebo group versus 15.0% (n = 421/2815) in the belimumab group (Figure 2). In addition, the proportion of patients who experienced ≥1 study drug-related SAE was 4.6% (n = 63/1355) in the placebo group versus 3.7% (n = 103/2815) in the belimumab group. The most frequently reported SAEs in both the placebo and belimumab groups by MedDRA system organ class were infections and infestations (placebo: 5.9% [n = 80/1355]; belimumab: 5.4% [n = 151/2815]), renal and urinary disorders (excluding urinary tract infections [included in infections and infestations]; placebo: 2.2% [n = 30/1355]; belimumab: 1.7% [n = 48/2815]), and musculoskeletal and connective tissue disorders (placebo: 2.1% [n = 28/1355]; belimumab: 1.7% [n = 48/2815]; Table 3). The most common items recorded for infections and infestations by preferred term were pneumonia (placebo: 1.3% [n = 18/1355]; belimumab: 0.8% [n = 22/2815]),

Table 1. Patient disposition.

	Placebo (IV + SC)	Belimumab (IV + SC)
	N = 1355	N = 2815
Completed Week-52 visit, n (%)	1038 (76.6)	2280 (81.0)
Withdrawn prior to week 52, n (%)	317 (23.4)	535 (19.0)
Patient request	71 (5.2)	108 (3.8)
AE	97 (7.2)	169 (6.0)
Disease progression/lack of efficacy	62 (4.6)	90 (3.2)
Lost to follow-up	13 (1.0)	42 (1.5)
Lack of compliance	11 (0.8)	15 (0.5)
Protocol deviation	18 (1.3)	27 (1.0)
Physician decision	23 (1.7)	36 (1.3)
Study terminated by sponsor[a]	3 (0.2)	5 (0.2)
Other[b]	19 (1.4)	43 (1.5)

AE: adverse event; IV: intravenous; SC: subcutaneous.
[a]Site closure.
[b]For BLISS-NEA, defined as "patient reached protocol-defined stopping criteria."

Table 2. Baseline demographics, disease characteristics, and medication usage of the pooled safety analysis population.

	Placebo (IV + SC) N = 1355	Belimumab (IV + SC) N = 2815
Female, n (%)	1268 (93.6)	2661 (94.5)
Age (years), mean (SD)	37·8 (12.0)	37·5 (11.5)
Age category (years), n (%)		
≤45	1011 (74.6)	2098 (74.5)
>46 to <65	317 (23.4)	681 (24.2)
≥65	27 (2.0)	36 (1.3)
Race, n (%)[a]		
White	516 (38.1)	1100 (39.1)
Asian[b]	418 (30.8)	836 (29.7)
Black African ancestry	269 (19.9)	568 (20.2)
American Indian or Alaskan native[c]	149 (11.0)	307 (10.9)
Native Hawaiian or other Pacific Islander	3 (0.2)	4 (0.1)
Multiracial	15 (1.1)	25 (0.9)
Hispanic or Latino, n (%)	373 (27.5)	765 (27.2)
SLE duration (years)[d], mean (SD)	6·8 (6.6)	6·7 (6.6)
SELENA-SLEDAI category, n (%)		
≤9	612 (45.2)	1315 (46.7)
≥10	743 (54.8)	1500 (53.3)
SELENA-SLEDAI score, mean (SD)	10·0 (3.8)	9·9 (3.7)
SLICC/ACR damage index score, n	1242	2476
Mean (SD)	0·6 (1.1)	0·6 (1.1)
Complement levels[e], n (%)		
Low	750 (55.4)	1587 (56.4)
Not low	605 (44.6)	1228 (43.6)
Anti-dsDNA antibodies[f], n (%)		
High	920 (67.9)	1932 (68.6)
Not high	435 (32.1)	883 (31.4)
Study drug exposure duration (days)[g], mean (SD)	325·3 (97.4)	334·1 (92.6)
SLE medication use, n (%)		
Any CS use	1184 (87.4)	2404 (85.4)
Any antimalarial use	956 (70.6)	1934 (68.7)
Any immunosuppressant use	712 (52.5)	1443 (51.3)
Average daily prednisone-equivalent dose, mg/day, mean (SD)	12·0 (9.7)	11·4 (9.6)
Average daily prednisone-equivalent dose, mg/day, n (%)		
0	171 (12.6)	411 (14.6)
>0–≤7.5	351 (25.9)	719 (25.5)
>7.5	833 (61.5)	1685 (59.9)

CS: corticosteroid; dsDNA: double-stranded deoxyribonucleic acid; IV: intravenous; SC: subcutaneous; SD: standard deviation; SELENA-SLEDAI: Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index; SLE: systemic lupus erythematosus; SLICC/ACR: Systemic Lupus International Collaborating Clinics/American College of Rheumatology.
[a]Patients who checked > one race category are counted under the individual category as well as the multiracial category.
[b]A patient of East Asian, Southeast Asian, Central/South Asian, or Japanese heritage, Asian heritage unknown or mixed Asian race.
[c]A patient having origins in any of the original peoples of North, Central, or South America.
[d]Duration defined as (treatment start date − SLE diagnosis date + 1).
[e]Low = C3 or C4 values below the lower limit of normal.
[f]High = anti-dsDNA ≥30 IU/mL.
[g]Duration of exposure (days) = (last injection date − first injection date + 7) for SC, and (last infusion date − first infusion date + 28) for IV. Only complete dates are used when calculating duration of exposure. First and last injection/infusion dates will have been used, regardless of any missed doses.

urinary tract infection (placebo: 0.6% [n = 8/1355]; belimumab: 0.5% [n = 13/2815]), and cellulitis (placebo: 0.4% [n = 5/1355]; belimumab: 0.5% [n = 14/2815]). The most common items recorded for renal and urinary disorders by preferred term were LN (placebo: 1.0% [n = 13/1355]; belimumab: 0.7% [n = 20/2815]), proteinuria (placebo: 0.4% [n = 5/1355]; belimumab: 0.2% [n = 5/2815]), and acute kidney injury (placebo: 0.3% [n = 4/1355];
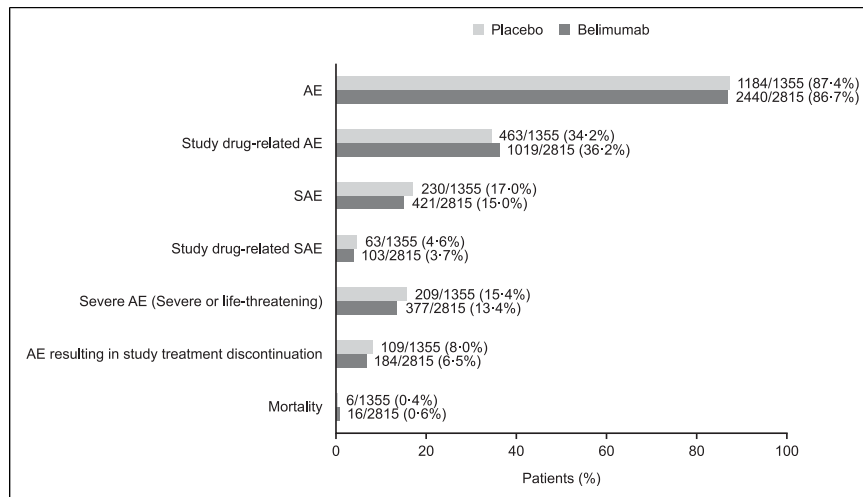
Figure 2. Summary of AEs, SAEs, and mortality in the pooled safety analysis population by treatment group.
AE: adverse event; SAE: serious adverse event.

belimumab: 0.2% [n = 5/2815]). Finally, the most common items recorded for musculoskeletal and connective tissue disorders by preferred term were SLE arthritis (placebo: 0.4% [n = 6/1355]; belimumab: 0.3% [n = 8/2815]), osteonecrosis (placebo: <0.1% [n = 1/1355]; belimumab: 0.2% [n = 5/2815]), and arthralgia (placebo: 0.1% [n = 2/1355]; belimumab: 0.1% [n = 4/2815]).

A similar proportion of patients experienced ≥1 severe AE in the placebo and belimumab groups (15.4% [n = 209/1355] and 13.4% [n = 377/2815], respectively; Figure 2). The incidence of AEs resulting in study treatment discontinuation was similar in the placebo and belimumab groups (8.0% [n = 109/1355] and 6.5% [n = 184/2815], respectively). The proportion of patients who experienced pregnancy, puerperium, or perinatal conditions was 0.4% (n = 5/1355) in the placebo group versus 0.5% (n = 14/2815) in the belimumab group. Further evaluation of any potential effect of belimumab on pregnancy will be provided in a separate publication.

Adverse events of special interest

A greater proportion of patients experienced post-infusion/injection systemic reactions with belimumab compared with placebo (10.2% [n = 286/2815] vs 8.1% [n = 110/1355], respectively). The proportion of patients experiencing malignancy (placebo: 0.2% [n = 3/1355]; belimumab: 0.4% [n = 12/2815]) AESI was similar between treatment groups. The incidence of depression, including mood disorders and anxiety, was 6.8% (n = 92/1355) with placebo versus 7.3% (n = 205/2815) in the belimumab group (difference: 0.5%; Table 3). The proportion of patients experiencing suicide/self-injury (placebo: 0.3% [n = 4/1355]; belimumab: 0.3% [n = 8/2815]) AESI was similar between treatment groups.

The reported suicide/self-injury events by preferred term included suicidal ideation (placebo: <0.1% [n = 1/1355]; belimumab: <0.1% [n = 2/2815]), depression suicidal (placebo: <0.1% [n = 1/1355]; belimumab: 0.0% [n = 0/2815]), intentional self-injury (placebo: <0.1% [n = 1/1355]; belimumab: 0.0% [n = 0/2815]), suicide attempt (placebo: <0.1% [n = 1/1355]; belimumab: 0.0% [n = 0/2815]), and completed suicide (placebo: 0.0% [n = 0/1355]; belimumab: <0.1% [n = 2/2815]). One case of suicidal ideation which occurred in the belimumab group was considered study drug related. The incidence of all infections of special interest, including herpes zoster, in the placebo group (7.2% [n = 97/1355]) was similar to belimumab (6.1% [n = 173/2815]) (Table 3).

Mortality

Rate of mortality in the placebo and belimumab groups was similar (0.4% [n = 6/1355] vs 0.6% [n = 16/2815], respectively; Figure 2). The most common reasons for mortality included infections (placebo: <0.1% [n = 1/1355]; belimumab: 0.3% [n = 9/2815]) and vascular events (placebo: 0.1% [n = 2/1355]; belimumab: <0.1% [n = 2/2815]; Table 4).

Discussion

This post hoc pooled analysis of six randomized belimumab clinical trials evaluated Week 52 safety data from a large and diverse population of patients with SLE that includes a high proportion of patients from Northeast Asia (~30%) and of Black African ancestry (~20%). Overall, the safety profile of belimumab over 52 weeks was similar to that of placebo, with similar rates of AEs, SAEs, most AESI, and mortality,

Table 3. SAEs (experienced by ≥1% patients) by system organ class and summary of AESIs in the pooled safety analysis population by treatment group.

n (%)	Placebo (IV + SC) N = 1355	Belimumab (IV + SC) N = 2815
Any SAE	230 (17.0)	421 (15.0)
Infections and infestations[a]	80 (5.9)	151 (5.4)
Renal and urinary disorders	30 (2.2)	48 (1.7)
Musculoskeletal and connective tissue disorders	28 (2.1)	48 (1.7)
Gastrointestinal disorders	26 (1.9)	45 (1.6)
Nervous system disorders	19 (1.4)	42 (1.5)
General disorders and administration site conditions	23 (1.7)	34 (1.2)
Respiratory, thoracic, and mediastinal disorders	19 (1.4)	30 (1.1)
Injury, poisoning, and procedural complications	13 (1.0)	31 (1.1)
Cardiac disorders	20 (1.5)	28 (1.0)
Vascular disorders	16 (1.2)	29 (1.0)
Blood and lymphatic system disorders	15 (1.1)	21 (0.7)
AESI		
Post-infusion/injection systemic reactions[b,c]	110 (8.1)	286 (10.2)
Serious post-infusion/injection systemic reaction	2 (0.1)	13 (0.5)
All infections of special interest (opportunistic infections, herpes zoster, tuberculosis, sepsis)[b]	97 (7.2)	173 (6.1)
Serious infections of special interest	17 (1.3)	40 (1.4)
Opportunistic infections	92 (6.8)	157 (5.6)
Serious opportunistic infections	14 (1.0)	25 (0.9)
Active tuberculosis	5 (0.4)	4 (0.1)
Serious active tuberculosis	3 (0.2)	3 (0.1)
Herpes zoster	59 (4.4)	106 (3.8)
Serious herpes zoster	5 (0.4)	15 (0.5)
Sepsis	10 (0.7)	20 (0.7)
Serious sepsis	6 (0.4)	18 (0.6)
Malignancies excluding NMSC[b]	2 (0.1)	8 (0.3)
Malignancies including NMSC[b]	3 (0.2)	12 (0.4)
Solid tumor	2 (0.1)	8 (0.3)
Hematological	0	0
All skin	1 (<0.1)	4 (0.1)
NMSC	1 (<0.1)	4 (0.1)
Excluding NMSC	0	0
Depression[b,d]	92 (6.8)	205 (7.3)
Serious depression	2 (0.1)	6 (0.2)
Suicide/self-injury[e]	4 (0.3)	8 (0.3)
Serious suicide/self-injury	4 (0.3)	4 (0.1)

AESI: adverse events of special interest; IV: intravenous; MedDRA: Medical Dictionary for Regulatory Activities; NMSC: non-melanoma skin cancer; SAE: serious adverse event; SC: subcutaneous.
[a]According to the MedDRA infections and infestations system organ class.
[b]Per custom MedDRA query.
[c]Occurring on or within 3 days of infusion/injection date.
[d]Including mood disorders and anxiety.
[e]Per standard MedDRA query.

and study retention rates were high (withdrawal rate ~20%). The most common SAEs by system organ class were infections and infestations, renal and urinary disorders, and musculoskeletal and connective tissue disorders. However, several items listed as SAEs, such as SLE arthritis and erythematosus rash, could indicate flaring of the disease rather than a side effect of treatment. No unexpected safety findings were observed throughout the pooled trials; however, a slightly higher proportion of patients experienced post-infusion/injection systemic reactions with

Table 4. Summary of mortality in the pooled safety analysis population by treatment group and MedDRA preferred term

Category, n (%)	Placebo (IV + SC) N = 1355	Belimumab (IV + SC) N = 2815
Mortality	6 (0.4)	16 (0.6)
Infectious	1 (<0.1)	9 (0.3)
Bacterial sepsis	0 (0)	2 (<0.1)
Pneumonia	0 (0)	1 (<0.1)
Sepsis	0 (0)	1 (<0.1)
Cardiac arrest	1 (<0.1)	0 (0)
Diarrhea infectious	0 (0)	1 (<0.1)
Meningitis	0 (0)	1 (<0.1)
Respiratory failure	0 (0)	1 (<0.1)
Tuberculosis of central nervous system	0 (0)	1 (<0.1)
Urosepsis	0 (0)	1 (<0.1)
Vascular	2 (0.1)	2 (<0.1)
Cardiac arrest	1 (<0.1)	0 (0)
Ischemic stroke	0 (0)	1 (<0.1)
Myocardial infarction	1 (<0.1)	0 (0)
Respiratory failure	0 (0)	1 (<0.1)
Unknown	2 (0.1)	1 (<0.1)
SLE-related	1 (<0.1)	1 (<0.1)
Cardiac arrest	0 (0)	1 (<0.1)
Thrombocytopenia	1 (<0.1)	0 (0)
Suicide	0 (0)	2 (<0.1)
Malignancy	0 (0)	1 (<0.1)
Ovarian cancer	0 (0)	1 (<0.1)

IV: intravenous; MedDRA: Medical Dictionary for Regulatory Activities; SC: subcutaneous.

belimumab versus placebo. The pooled safety data were consistent with those observed in the individual studies, supporting the use of belimumab for SLE across a diverse adult patient population.[12–17]

The incidence of all-cause mortality and AESI with belimumab versus placebo in patients with autoantibody-positive SLE has also been investigated in the multicenter, double-blind, randomized, Phase 4 BASE study.[19] BASE did not require baseline disease activity as part of the inclusion criteria in order to better reflect clinical practice compared with previous SLE trials, such as those included in this pooled analysis.[19] The number of patients with SLE included in BASE (placebo, n = 2001; belimumab, n = 2002) is the largest to date, and is similar to that in the current analysis; taken together (placebo: N = 3356; belimumab: N = 4817), this makes belimumab one of the most highly studied drugs overall for safety in the treatment of SLE.[19] The majority of patients in BASE were White (only 8% of patients were of Black African ancestry), whereas the current analysis had a more racially balanced population (∼30% Asian and ∼20% of Black African ancestry). In BASE, the incidence of serious infusion or hypersensitivity reactions (placebo: 0.1% [n = 2/2001]; belimumab: 0.4% [n = 8/2002]) was slightly higher with belimumab versus

placebo, consistent with the findings of this pooled analysis. Similarly, the incidence of serious depression (placebo: 0.1% [n = 1/2001]; belimumab: 0.4% [n = 7/2002]) was slightly higher with belimumab versus placebo, which was also the case for depression (including mood disorders and anxiety) in the current study. However, unlike BASE, where a greater proportion of patients in the belimumab versus placebo group had sponsor-adjudicated serious suicide or self-injury (0.75% [n = 15/2002] vs 0.25 [n = 5/2001]), the incidence of these events was 0.3% for both treatment groups in the current analysis. The mortality rate in this pooled analysis was also similar between treatment groups, consistent with the BASE study (placebo: 0.4% [n = 8/2001]; belimumab: 0.5% [n = 10/2002]).[19]

The current analysis supports the positive benefit–risk profile of belimumab over 52 weeks of treatment and complements long-term clinical trials and real-world observational studies, providing extensive insights into the safety of belimumab over a longer period. Further to the primary BASE publication, reporting results at 52 weeks, mortality rates were similar during the study period (Year 1) and Years 2 and 3 of post-treatment follow-up, whilst malignancy rates for Year 3 of follow-up were numerically higher than in Year 2, but similar to during the study

(Year 1).[21,22] No new safety concerns were identified during Years 2 and 3 of follow-up off-treatment, providing continued support for the safety of belimumab in treatment of SLE.[21,22]

In a Phase 3 extension study of patients with SLE treated with belimumab, belimumab had a stable safety profile with low organ damage accrual at study Year 8 on-treatment.[23] In addition, the annual AE incidence, including SAEs, remained stable or decreased throughout the duration of the study. Of note, depression, suicide and/or self-injury rates decreased, and there were no completed suicides.[23] Additionally, a long-term, open-label extension study reporting safety data for up to 13 years of belimumab treatment (plus ST) demonstrated a safety profile consistent with the individual clinical trials included in this pooled analysis.[12,13,17,24,25] Of note, there was no increase in the incidence of AEs over time, suggesting that safety outcomes after 52 weeks are typically maintained over longer periods.[24] A long-term, open-label continuation study of Japanese patients who completed the BLISS-NEA or BLISS-SC studies demonstrated that a favorable safety profile for belimumab was maintained for ≤7 years, with only 32.4% of patients experiencing treatment-emergent SAEs, which is lower than the incidence rate in the current analysis.[26] However, unlike the current study, no malignancies, serious post-infusion/injection systemic reactions, or suicidality were reported.[26]

The safety results of the current pooled analysis are also consistent with those of a pediatric population.[27] The PLUTO Phase 2 randomized clinical trial demonstrated the safety and efficacy of belimumab plus ST in children aged 5–17 years with active childhood-onset SLE.[27] In both the current study and the PLUTO study, there were similar incidences of AEs and SAEs between treatment groups.[27]

Consistent with the current analysis, the 104-week BLISS-LN trial of belimumab in the treatment of patients with SLE and biopsy-confirmed active LN requiring induction therapy, reported a similar safety profile of belimumab combined with ST compared with ST alone.[18] Incidence of AEs, SAEs, AESI (malignancy, post-infusion reactions, infections of special interest, and depression/suicide/self-injury), and mortality were similar between the placebo and belimumab groups.[18] Similar to the current study, the most common SAE by system organ class was infections and infestations.[18] Patients in BLISS-LN also had a reduced risk of kidney-related events or mortality in the belimumab group compared with placebo.[18] Furthermore, a post hoc analysis of the BLISS-LN study provided additional safety data on the effect of different STs, demonstrating that patients receiving cyclophosphamide/azathioprine had a lower risk of kidney-related events or mortality compared with those who received mycophenolate mofetil.[28] Therefore, the current analysis, together with findings from BASE, BLISS-LN, and open-label extension

studies, provide a comprehensive insight into the safety and tolerability of belimumab. Data from the large, diverse population of the current study also helps to rule out any rare safety signals that were not identified in the smaller individual trial populations; there were no indications of any such signals.

As the strict inclusion and exclusion criteria as well as requirements for consistent concomitant medication use can limit the generalizability of clinical trial data, real-world belimumab studies have also been performed.[29–32] A real-world belimumab study by Gatto et al. of 466 patients with active SLE observed AEs in 58.2% of patients over a median follow-up period of 18 months,[29] which was lower than in the current analysis. Furthermore, only 20.7% of these patients experienced a severe AE, no deaths were observed, and only 12.4% of all patients in the study discontinued belimumab due to incidence of AEs.[29] These results are similar to or higher than the current analysis, in which 13.4% of the belimumab group experienced severe AEs, the mortality rate was 0.6%, and 6.0% withdrew from the study due to incidence of AEs. Similarly, in the retrospective observational real-life OBSErve studies, while detailed safety data were not collected, the low number of discontinuations of belimumab due to AEs (4.3–5.9%) indicated good tolerability and was similar to the current analysis.[31,32]

Limitations of the current analysis include that all results are descriptive, and that no subgroup analyses were conducted. Differences in the recruitment strategies of the included studies may have also introduced demographical inconsistencies between the pooled studies. For example, patients in EMBRACE were asked whether they self-identified as black race, meaning that some patients who did not primarily identify as being of black race were instead counted as mixed race;[16] this was not the case for the other five trials. Furthermore, patients with severe active LN and central nervous system lupus were excluded from all six studies, meaning that the pooled population might not be representative of the wider real-world SLE population. Similarly, the treatment period of 52 weeks may not be representative of typical belimumab treatment periods experienced by patients in the real world; as a result, no conclusions can be drawn about the long-term safety of belimumab from these data alone. The use of different doses and formulations of belimumab across the included studies also means that some nuances in the data may have been lost. Similarly, the 1 mg/kg belimumab IV dose included in BLISS-76, BLISS-52, and LBSL02, and the 4 mg/kg belimumab IV dose included in LBSL02 are not approved dosages for the treatment of SLE.

In conclusion, the safety results of this large, integrated analysis are consistent with those observed for the individual studies, BASE, BLISS-LN, and long-term extension studies, making belimumab one of the most highly studied

drugs for safety in the treatment of SLE. These findings add to the evidence base supporting a positive benefit–risk profile of belimumab in the treatment of adult patients with SLE.[12–19,23,24]

Author contributions

AH, **PM** and **DAR** contributed to the concept and design of the study. **DJW**, **TA**, **AS**, and **FZ** contributed to the acquisition of data. All authors contributed to the data analysis and interpretation.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: **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**, **HQ**, and **DAR** are employees of GSK and hold stocks and shares in the company. **PM** was an employee of GSK and held stocks and shares in the company at the time of the study. **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 been a paid speaker for GSK and has taken part in a GSK advisory board.

Data sharing

GSK is committed to publicly disclosing the results of GSK-sponsored clinical research that evaluates GSK medicines, and as such was involved in the decision to submit. Anonymized individual patient data and study documents can be requested for further research from www.clinicalstudydatarequest.com

Ethical approval

National Clinical Trial numbers, ClinicalTrials.gov: NCT00071487, NCT00424476, NCT00410384, NCT01345253, NCT01632241, NCT01484496

References

1. Fanouriakis A, Kostopoulou M, Alunno A, et al. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. *Ann Rheum Dis* 2019; 78: 736–745.

2. Tunnicliffe DJ, Singh-Grewal D, Kim S, et al. Diagnosis, monitoring, and treatment of systemic lupus erythematosus: a systematic review of clinical practice guidelines. *Arthritis Care Res (Hoboken)* 2015; 67: 1440–1452.

3. Touma Z and Gladman DD. Current and future therapies for SLE: obstacles and recommendations for the development of novel treatments. *Lupus Sci Med* 2017; 4: e000239.

4. Tamirou F, Husson SN, Gruson D, et al. Brief report: the Euro-lupus low-dose intravenous cyclophosphamide regimen does not impact the ovarian reserve, as measured by serum levels of anti-Mullerian hormone. *Arthritis Rheumatol* 2017; 69: 1267–1271.

5. Hsu CY, Lin MS, Su YJ, et al. Cumulative immunosuppressant exposure is associated with diversified cancer risk among 14.832 patients with systemic lupus erythematosus: a nested case-control study. *Rheumatology (Oxford)* 2017; 56: 620–628.

6. Halpern WG, Lappin P, Zanardi T, et al. Chronic administration of belimumab, a BLyS antagonist, decreases tissue and peripheral blood B-lymphocyte populations in cynomolgus monkeys: pharmacokinetic, pharmacodynamic, and toxicologic effects. *Toxicol Sci* 2006; 91: 586–599.

7. Di Battista M, Marcucci E, Elefante E, et al. One year in review 2018: systemic lupus erythematosus. *Clin Exp Rheumatol* 2018; 36: 763–777.

8. GSK. Belimumab European Union summary of product characteristics, 2016.

9. GSK. Belimumab Japan results of deliberation, 2017.

10. GSK. Belimumab Canada product monograph, 2019.

11. GSK. Belimumab (Benlysta) – Prescribing information US, 2021.

12. Furie R, Petri M, Zamani O, et al. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. *Arthritis Rheum* 2011; 63: 3918–3930.

13. Navarra SV, Guzmán RM, Gallacher AE, et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. *Lancet* 2011; 377: 721–731.

14. Stohl W, Schwarting A, Okada M, et al. Efficacy and safety of subcutaneous belimumab in systemic lupus erythematosus: a fifty-two-week randomized, double-blind, placebo-controlled study. *Arthritis Rheumatol* 2017; 69: 1016–1027.

15. Zhang F, Bae SC, Bass D, et al. A pivotal phase III, randomised, placebo-controlled study of belimumab in patients with systemic lupus erythematosus located in China, Japan and South Korea. *Ann Rheum Dis* 2018; 77: 355–363.

16. Ginzler E, Guedes Barbosa LS, D'Cruz D, et al. Phase III/IV, randomized, fifty-two-week study of the efficacy and safety of belimumab in patients of black African ancestry with systemic lupus erythematosus. *Arthritis Rheumatol* 2022; 74: 112–123.

17. Wallace DJ, Stohl W, Furie RA, et al. A phase II, randomized, double-blind, placebo-controlled, dose-ranging study of belimumab in patients with active systemic lupus erythematosus. *Arthritis Rheum* 2009; 61: 1168–1178.

18. Furie R, Rovin BH, Houssiau F, et al. Two-year, randomized, controlled trial of belimumab in lupus nephritis. *N Engl J Med* 2020; 383: 1117–1128.

19. Sheikh S, Scheinberg MA, Wei JC, et al. Mortality and adverse events of special interest with intravenous belimumab for adults with active, autoantibody-positive systemic lupus erythematosus (BASE): a multicentre, double-blind, randomised, placebo-controlled, phase 4 trial. *Lancet Rheumatol* 2021; 3: E122–E130.

20. Hochberg M. Updating the American college of rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheumatol* 1997; 40: 1725.

21. Sheikh S, Scheinberg M, Wei JCC, et al. Ab0288 safety of belimumab in patients with active systemic lupus erythematosus: year 2 follow-up of a large phase 4, randomised, double-blind, placebo-controlled study. *Ann Rheum Dis* 2021; 80: 1170–1171.

22. Sheikh S, Wei C, Tegzova D, et al. Year-3 Observational follow-up of belimumab safety (mortality and malignancies) in patients with SLE who completed a Phase 4, 52-week, randomized, double-blind placebo-controlled safety study. *ACR Convergence 2021*. 2021.

23. van Vollenhoven RF, Navarra SV, Levy RA, et al. Long-term safety and limited organ damage in patients with systemic lupus erythematosus treated with belimumab: a Phase III study extension. *Rheumatology (Oxford)* 2020; 59: 281–291.

24. Wallace DJ, Ginzler EM, Merrill JT, et al. Safety and efficacy of belimumab plus standard therapy for up to thirteen years in patients with systemic lupus erythematosus. *Arthritis Rheumatol* 2019; 71: 1125–1134.

25. Furie RA, Wallace DJ, Aranow C, et al. Long-term safety and efficacy of belimumab in patients with systemic lupus erythematosus: a continuation of a seventy-six-week phase III parent study in the United States. *Arthritis Rheumatol* 2018; 70: 868–877.

26. Tanaka Y, Curtis P, DeRose K, et al. Long-term safety and efficacy of belimumab in Japanese patients with SLE: a 7-year open-label continuation study. *Mod Rheumatol* 2021. Online ahead of print.

27. Brunner HI, Abud-Mendoza C, Viola DO, et al. Safety and efficacy of intravenous belimumab in children with systemic lupus erythematosus: results from a randomised, placebo-controlled trial. *Ann Rheum Dis* 2020; 79: 1340–1348.

28. Rovin BH, Furie R, Teng YKO, et al. A secondary analysis of the Belimumab international study in lupus nephritis trial examined effects of belimumab on kidney outcomes and preservation of kidney function in patients with lupus nephritis. *Kidney Int* 2021; 101: 304–413.

29. Gatto M, Saccon F, Zen M, et al. Early disease and low baseline damage as predictors of response to belimumab in patients with systemic lupus erythematosus in a real-life setting. *Arthritis Rheumatol* 2020; 72: 1314–1324.

30. Anjo C, Mascaró JM, Jr, Espinosa G, et al. Effectiveness and safety of belimumab in patients with systemic lupus erythematosus in a real-world setting. *Scand J Rheumatol* 2019; 48: 469–473.

31. Schwarting A, Schroeder JO, Alexander T, et al. First real-world insights into belimumab use and outcomes in routine clinical care of systemic lupus erythematosus in Germany: results from the OBSErve Germany study. *Rheumatol Ther* 2016; 3: 271–290.

32. Collins CE, Cortes-Hernandez J, Garcia MA, et al. Real-world effectiveness of belimumab in the treatment of systemic lupus erythematosus: pooled analysis of multi-country data from the OBSErve studies. *Rheumatol Ther* 2020; 7: 949–965.