



# 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

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## Summary

**Background** Belimumab is approved for the treatment of active systemic lupus erythematosus (SLE). Although clinical trials showed a favourable benefit–risk profile, numerical differences in the incidence of mortality and adverse events of special interest (AESIs) have been reported. We assessed the frequency of these events in patients with SLE receiving belimumab or placebo plus standard therapy.

**Methods** BASE was a double-blind, randomised, placebo-controlled, phase 4 trial done in 33 countries. Adults with active SLE were randomly assigned (1:1) to receive intravenous belimumab (10 mg/kg) or placebo, plus standard therapy, for 48 weeks. The primary endpoints were incidences of all-cause mortality and AESIs during the on-treatment period (first-to-last study drug dose + 28 days). Safety analyses were done in the as-treated population (patients grouped by actual treatment received >50% of the time). This study was registered with ClinicalTrials.gov (NCT01705977).

**Findings** Between Nov 27, 2012, and July 28, 2017, we randomly assigned 4018 patients. The as-treated population included 2002 patients in the belimumab group versus 2001 in the placebo group. Ten (0·50%) patients in the belimumab group died versus eight (0·40%) in the placebo group (difference 0·10%, 95% CI –0·31 to 0·51). Incidences were similar in the belimumab and placebo groups for serious infections (75 [3·75%] of 2002 vs 82 [4·10%] of 2001; difference –0·35%, 95% CI –1·55 to 0·85), opportunistic infections and other infections of interest (36 [1·80%] vs 50 [2·50%]; –0·70%, –1·60 to 0·20), non-melanoma skin cancers (4 [0·20%] vs 3 [0·15%]; 0·05%, –0·21 to 0·31) and other malignancies (5 [0·25%] vs 5 [0·25%]; 0·00%, –0·31 to 0·31). A higher proportion of patients in the belimumab group than in the placebo group had infusion and hypersensitivity reactions (8 [0·40%] vs 2 [0·10%]; 0·30%, –0·01 to 0·61), serious depression (7 [0·35%] vs 1 [0·05%]; 0·30%, 0·02 to 0·58), treatment-emergent suicidality (28 [1·42%] of 1972 patients vs 23 [1·16%] of 1986; 0·26%, –0·44 to 0·96), and sponsor-adjudicated serious suicide or self-injury (15 [0·75%] of 1972 patients vs 5 [0·25%] of 1986; post hoc difference 0·50%, 0·06 to 0·94).

**Interpretation** In line with previously published data, incidences of all-cause mortality and AESIs were similar in patients given belimumab and placebo, except for serious infusion or hypersensitivity reactions, serious depression, treatment-emergent suicidality, and sponsor-adjudicated serious suicide or self-injury events.

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## Introduction

Belimumab is a recombinant, IgG1λ human monoclonal antibody that antagonises soluble B-cell activating factor (BAFF, also known as B lymphocyte stimulator, or BLyS).<sup>1</sup> In Europe, North America, Japan, and China, both intravenous and subcutaneous formulations of belimumab are approved for use in patients aged 18 years or older with active, autoantibody-positive systemic lupus erythematosus (SLE) who are receiving standard therapy.<sup>1,2</sup> In the USA

and EU, intravenous belimumab is also indicated for use in children aged 5 years or older.<sup>1,2</sup>

Although belimumab was generally well tolerated in adults with SLE during randomised phase 3 trials,<sup>3–5</sup> numerical differences in the incidences of mortality and some adverse events, including serious infusion and hypersensitivity reactions, serious infections, and some psychiatric events, were observed between patients receiving belimumab and those receiving placebo. There is also a

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## Research in context

### Evidence before this study

Treatment for systemic lupus erythematosus (SLE) is guided by an individual's disease manifestations. Evidence suggests that B-cell activating factor (BAFF) has a genetic association with SLE, and BAFF concentrations are correlated with disease activity. Belimumab, the first biological drug to be approved as an add-on treatment for active autoantibody-positive SLE, binds to and neutralises soluble BAFF, thereby down-modulating the B-cell hyperactivity associated with SLE. Because numerical differences in the incidences of mortality and adverse events of special interest, such as serious infusion and hypersensitivity reactions, serious infections, and psychiatric events, were observed in the initial phase 3 trials of belimumab, further investigation was warranted in a large cohort of patients with SLE.

### Added value of this study

This double-blind, placebo-controlled, 52-week study (BASE) is the largest study of patients with SLE to date, involving

more than 4000 participants. BASE did not have eligibility criteria for SLE disease activity and therefore may better reflect clinical practice compared with the previous phase 3 efficacy and safety trials of belimumab. There was no difference of clinical concern in mortality between belimumab and placebo. The incidences of serious infusion or hypersensitivity reactions, serious depression, and suicidality were higher among patients who received belimumab than among those who received placebo, although the numbers of events were small.

### Implications of all the available evidence

Awareness of these adverse events should be encouraged among physicians and patients to optimise individual clinical management. The safety findings in this study were generally consistent with previous studies and experience in clinical practice. The overall benefit–risk profile for belimumab remains positive.

theoretically increased risk of malignancy and opportunistic infections based on the immunomodulatory activity of belimumab. Due to the low frequency of these adverse events of special interest (AESIs) in the phase 3 trials, further investigation was warranted in a large group of patients with SLE treated with belimumab or placebo.

The aim of this trial, the largest clinical study in SLE to date, was to assess all-cause mortality and protocol-defined AESIs in adult patients with active, autoantibody-positive SLE receiving intravenous belimumab or placebo, plus standard therapy. This trial was a post-approval study required by both the European Medicines Agency and the US Food and Drug Administration.

## Methods

### Study design and participants

This study (BASE) was a 52-week, phase 4, randomised, double-blind, placebo-controlled trial done in 259 hospitals and clinical research centres in 33 countries worldwide (north, central, and south America, Europe, Australia, and Asia; appendix pp 6–10). The study protocol is available online from the GSK Clinical Study register (number 115467).

We included patients aged 18 years or older who met the American College of Rheumatology revised criteria for SLE<sup>6,7</sup> and had active, autoantibody-positive SLE (defined as the presence of anti-nuclear antibodies  $\geq 1:80$  or anti-dsDNA antibodies  $\geq 30$  IU/mL). All patients were receiving standard therapy (corticosteroids, immunomodulatory agents, or antimalarial drugs). There were no exclusion criteria based on psychiatric symptoms. Full eligibility criteria are provided in the appendix (pp 1–2).

Patients who discontinued treatment were encouraged to continue attending regular visits until week 52 to

facilitate capture of safety information. In addition, any patients who withdrew consent before week 52 were approached to be re-consented to assess mortality and malignancy at the end of the 52-week period and during the 2–5-year follow-up period.

The study was approved by local institutional review boards or ethics committees and all patients provided written informed consent. The study was done in accordance with International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Good Clinical Practice ethical principles, and the Declaration of Helsinki.

### Randomisation and masking

Principal investigators and research study teams at each site were responsible for patient enrolment. Patients were randomly assigned (1:1) to belimumab or placebo. Randomisation was stratified by geographical region (USA/Canada vs central America/south America/Mexico vs Europe/Australia vs Asia), baseline Safety of Estrogens in Lupus Erythematosus National Assessment-SLE Disease Activity Index (SELENA-SLEDAI) score ( $\leq 9$  vs  $\geq 10$ ), and corticosteroid dose ( $\leq 7.5$  mg/day vs  $>7.5$  mg per day). The randomisation was generated by Almac using a block size of four for each of the 16 strata and implemented using a central interactive response system. Except for a limited number of safety oversight personnel and the site pharmacist or designee who dispensed the blinded study drugs, all other study site personnel, patients, the sponsor, and the contract research organisation were masked to the treatment assignment. Treatment allocation could be unmasked by the investigator or treating physician in the event of a serious medical emergency or medical condition.

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See Online for appendix

### Procedures

Patients received either belimumab (10 mg/kg, intravenously) or placebo over approximately a 1 h period on days 0, 14, 28, then approximately every 28 days until week 48. A final in-clinic visit was done at week 52. The regimen for standard therapy was based on a patient's disease manifestations and was in accordance with the country's and institution's approach to standard therapy for the patient's disease signs and symptoms but was consistent with the protocol's inclusion and exclusion criteria.

### Outcomes

The primary endpoints were the incidences of all-cause mortality and prespecified AESIs up to 52 weeks. The AESIs were serious infections, opportunistic infections and other infections of interest (herpes zoster, tuberculosis or tuberculosis reactivation, sepsis), malignancies (excluding non-melanoma skin cancer), non-melanoma skin cancer, serious infusion and hypersensitivity reactions (defined as anaphylactic reaction occurring on or within 3 days of infusion), serious depression, and suicidality (assessed using the Columbia-Suicide Severity Rating Scale [C-SSRS],<sup>8</sup> which assesses serious and non-serious events). Serious depression and serious infusion and hypersensitivity reactions were identified using a broad search custom Medical Dictionary for Regulatory Activities [MedDRA] query (appendix pp 2–3) of serious adverse event data (MedDRA version 21.1). The C-SSRS was adapted and validated for the languages used in all participating countries. Patients had to have at least one on-study C-SSRS assessment in order to be included in analyses. Depression and suicide or self-injury, and suicide or self-injury alone, were also evaluated as Programme Safety Analysis Plan (PSAP)-defined AESIs. We collected data only for serious adverse events and protocol-defined AESIs.

The main efficacy endpoint was the percentage of patients receiving at least 7.5 mg per day corticosteroids at baseline whose mean corticosteroid dose to treat SLE was reduced by 25% or more from baseline to less than 7.5 mg per day during weeks 40–52 (ie, patients who were corticosteroid responders). Other efficacy endpoints were immunomodulatory medication use for SLE, percentage of patients admitted to hospital, and number of hospital admissions per patient. Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index<sup>9</sup> (SDI) change from baseline to week 52 was recorded to assess the accrual of damage in patients.

SLE disease activity score was not an eligibility criterion. We did not collect data on change in disease activity (including disease flares) and non-SLE medication use after baseline because the primary objective of the study focused on safety. Corticosteroid and immunosuppressant use were evaluated in the context of the protocol, which did not have specific restrictions on their use.

### Statistical analysis

There were no formal statistical hypotheses for the primary safety endpoints in this study. The main purpose was to provide an evaluation of the difference in incidence of all-cause mortality and all prespecified AESIs between the belimumab and placebo groups, with a two-sided 95% CI.

A target population of 5000 patients was originally planned to give  $\pm 0.46\%$  precision of the 95% CI for the between-group treatment difference for mortality, assuming a first-year mortality rate of 0.68% in both treatment groups. After the study began and following the completion of two additional randomised controlled trials of belimumab in SLE,<sup>3,10</sup> the mortality rate estimate was adjusted to 0.56%, leading to a revised target population of 4000 patients to provide  $\pm 0.46\%$  precision for the between-group treatment difference 95% CI for mortality. The request to change the sample size was made in December, 2016, when 304 sites from 33 countries had recruited 3459 participants. The randomised population was defined as all patients who were randomly assigned, with patients grouped according to the treatment that they were allocated to receive, regardless of actual treatment received. Safety analyses were done for the as-treated population (grouped according to the treatment that was received for more than 50% of doses), as the primary endpoints were safety endpoints. Secondary efficacy endpoints were analysed using the intention-to-treat population (anyone in the randomised population who received at least one dose of study drug, grouped according to the treatment that a patient was assigned to receive, regardless of the actual treatment received).

The primary analyses of mortality and AESIs used data from the on-treatment period, which was defined as the period between first dose and last dose of the drug, plus 28 days (or death). Supportive analyses used the on-study period, which was defined as the period between first dose and the end of week 52 of study follow-up (or death) and therefore includes both on-treatment and off-treatment data for some patients. Because the C-SSRS assessment covered the period since last visit, the first assessment at the visit after the last dose of treatment included part of the on-treatment period (to +28 days post-dose) and potentially part of the off-treatment portion of the on-study period. Therefore, C-SSRS analyses focused on the on-study period.

The differences between treatment groups for all-cause mortality and AESIs were evaluated with two-sided 95% CIs using the simple asymptotic  $\chi^2$  (Pearson) method. We constructed forest plots for the percentage of patients with an event for mortality and other AESIs for the on-treatment period. We used a Kaplan-Meier plot, including standard error bands, for all-cause mortality for belimumab and placebo for the on-treatment and on-study periods to show the change in risk over time. Serious adverse events were summarised descriptively and coded according to MedDRA (version 21.1) preferred term and system organ class.

For the major efficacy endpoint (corticosteroid reductions), we compared the belimumab and placebo groups using a logistic regression model with independent variables of treatment group, baseline prednisone equivalent dose, and the randomisation stratification factors screening SELNA-SLEDAI score and region. Information on hospital admissions was derived from serious adverse event data and summarised descriptively.

We did post hoc analysis of the differences and associated 95% CIs between belimumab and placebo for on-treatment serious suicidal ideation or behaviour and self-injury events (per sponsor adjudication); on-study suicidal ideation and behaviour (C-SSRS); and infection-related mortality. In addition, event outcomes and follow-up for patients with on-study serious suicide or self-injury events (per sponsor adjudication) and demographic and baseline characteristics for patients who developed depression and suicide or self-injury events were summarised post hoc. Adjudication occurred before database release and unmasking and was done by the sponsor safety review team who evaluated patient safety case narratives for evidence of suicidal behaviour. We used SAS software for all analyses (version 9.4).

A descriptive interim analysis was done in December, 2016, by Statistics Collaborative (Washington, DC, USA) when at least 2000 patients had completed week 52. This analysis was solely for monitoring patients' safety and reporting event rates to health authorities. To maintain treatment masking within the study team, the interim analysis was handled by a sponsor firewall team who were independent from the study team. An independent data monitoring committee reviewed the unmasked safety data approximately every 6 months until database lock.

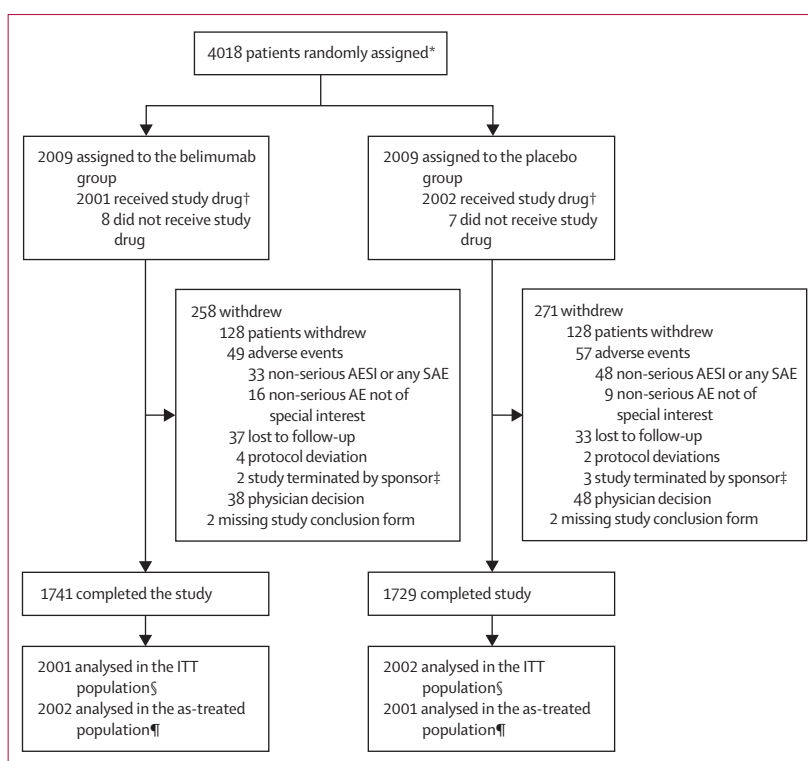
This study was registered with ClinicalTrials.gov (NCT01705977).

### Role of the funding source

The study sponsor had a role in study design, data collection, analysis and interpretation, and in the writing of the report. The sponsor did not place any restrictions on access to data or statements made in the report. The authors had full access to all study data and had final responsibility to submit for publication.

### Results

Recruitment took place between Nov 27, 2012, and July 28, 2017, and the last follow-up visit was completed on July 30, 2018. Of the 4018 patients in the randomised population, 4003 received at least one dose of study drug and were included in the intention-to-treat population (2001 in the belimumab group, 2002 in the placebo group; figure 1). The as-treated population consisted of 2002 belimumab-treated patients and 2001 placebo-treated patients (figure 1). 345 (17.24%) of 2001 belimumab-treated patients and 356 (17.78%) of 2002 placebo-treated patients in the intention-to-treat population prematurely



**Figure 1: Trial profile**

The number of patients screened for eligibility and the number excluded at this stage were not collected and are therefore not available. AESI=adverse event of special interest. ITT=intention-to-treat. SAE=serious adverse event.

\*4019 patients were randomised in the interactive response system, but one patient is not represented because their randomisation details were not entered into the database; the patient did not receive study agent.

†According to their treatment assignment; one patient was assigned to receive placebo but incorrectly received belimumab for >50% of the time, so they were included in different groups for different analyses: in the placebo group for the ITT analyses, and in the belimumab group for the as-treated analyses (included here as randomised).

‡Indicates site closure. §Patients were included in the ITT population if they were randomly assigned and received at least one dose of study drug, according to their randomised treatment group, regardless of what they actually received. ¶Patients were included in the as-treated population according to the actual treatment that the patient received most of the time (>50%).

discontinued study agent, and 258 (12.89%) patients receiving belimumab and 271 (13.54%) patients receiving placebo withdrew from the study. Patient's decision was the most common reason for withdrawal (figure 1) and for premature discontinuation of study drug (144 [7.20%] of 2001 in the belimumab group vs 138 [6.89%] of 2002 in the placebo group). In this group, patients mentioned issues with travel or location, and a lack of efficacy as the most common reasons for withdrawal in both treatment groups. At week 52, 88 (2.20%) of 4003 patients in the as-treated population were lost to follow-up or had unattainable mortality status.

Patient baseline demographics and clinical characteristics were generally similar in each group (table 1). In the intention-to-treat population, the median duration of exposure to randomly assigned treatment was 364 days (362–366) in the belimumab and 364 days (361–365) in the placebo group. Patient-year follow-up data were very similar for both treatment groups (on-treatment, 1825.8 patient-years in the belimumab group vs



	Belimumab group (n=2001)	Placebo group (n=2002)
Age (years)	40.4 (12.75)	40.8 (12.74)
Female	1848 (92.35%)	1853 (92.56%)
Weight (kg)	68.7 (18.11)	68.1 (17.67)
Median disease duration (IQR; years)	5.1 (1.6–10.6)	5.3 (1.8–11.2)*
SELENA-SLEDAI†		
Mean (SD)	7.8 (4.72)‡	7.9 (4.51)
≤9 (n, %)	1363 (68.12%)	1369 (68.38%)
≥10, (n, %)	638 (31.88%)	633 (31.62%)
Low complement and high anti-dsDNA binding	568 (28.39%)	584 (29.17%)
Average prednisone§ dose (mg/day) to treat SLE		
0	339 (16.94%)	363 (18.13%)
>0 to 7.5	676 (33.78%)	649 (32.42%)
>7.5	986 (49.28%)	990 (49.45%)
Current psychiatric disorder	241 (12.04%)	221 (11.04%)
Past psychiatric disorder	166 (8.30%)	151 (7.54%)

In the intention-to-treat population. Data are mean (SD) or n (%), unless stated otherwise. SELENA-SLEDAI=Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index. SLE=systemic lupus erythematosus. \*n=2001. †Per electronic case report form. ‡n=2000. §Corticosteroids were prednisone equivalent.

**Table 1: Baseline characteristics**

1825.4 patient-years in the placebo group; on-study, 1982.3 vs 1981.9); thus, we do not report mortality incidence per patient-year.

The incidence of all-cause mortality during the on-treatment period was similar in the belimumab group and placebo group. Ten (0.50%) of 2002 patients died in the belimumab group versus eight (0.40%) of 2001 in the placebo group; difference 0.10% (95% CI –0.31 to 0.51; figure 2). The on-treatment follow-up adjusted mortality rate was 0.55 per 100 person-years. Most on-treatment deaths in the belimumab group occurred between weeks 5 and 20; the accumulation of on-treatment deaths in the placebo group was relatively linear over the 52-week period (appendix p 4). Overall, 12 (0.60%) of 2002 patients in the belimumab group versus 11 (0.55%) of 2001 in the placebo group had serious adverse events that began during the on-treatment period and led to death; of these, five deaths (two in the belimumab group and three in the placebo group) occurred during the off-treatment period and so did not contribute to the number of deaths occurring during the on-treatment period (appendix p 4). Infection-related deaths (adjudicated by sponsor) were the most common cause of death on-treatment in the belimumab group (nine [0.45%] of 2002), while infection-related deaths (three [0.15%] of 2001) and vascular-related deaths (three [0.15%]) were the most common causes in the placebo group (appendix p 11). In a post hoc analysis, the difference in the incidences of infection-related deaths between belimumab and placebo was 0.30% (95% CI –0.04 to 0.64).

During the on-study period (including on-treatment and off-treatment data), the incidence of all-cause mortality was lower in the belimumab group than in the placebo group: 13 (0.65%) of 2002 patients died in the belimumab group versus 22 (1.10%) of 2001 in the placebo group; difference –0.45% (95% CI –1.03 to 0.13). There were fewer post-treatment deaths in the belimumab group than in the placebo group (three [0.15%] of 2002 vs 14 [0.70%] of 2001). Infection-related deaths (adjudicated by sponsor) were the most common cause of death in the on-study period (appendix p 11) and a post hoc analysis of time to infection-related mortality on-study is shown in the appendix (p 5).

Overall, incidences of most protocol-defined AESIs were similar in each group for the on-treatment period (figure 2). Results for on-study AESIs were consistent with those for on-treatment AESIs (data not shown).

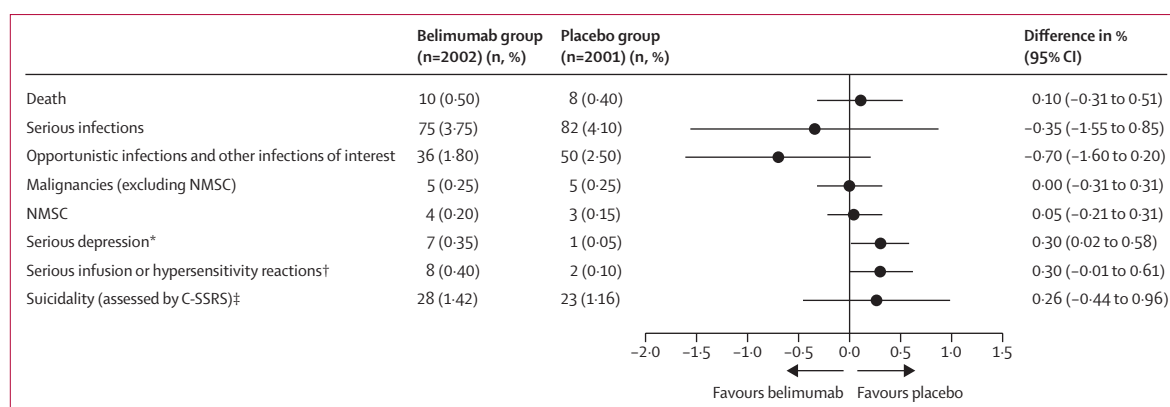
Of the AESIs, on-treatment serious infection events were reported for 75 (3.75%) of 2002 patients in the belimumab group and 82 (4.10%) of 2001 in the placebo group (difference –0.35%, 95% CI –1.55 to 0.85). Similarly, fewer patients in the belimumab group than in the placebo group had on-treatment opportunistic infections and other serious and non-serious infections of interest (36 [1.80%] of 2002 vs 50 [2.50%] of 2001; difference –0.70%, 95% CI –1.60 to 0.20). Of the opportunistic infections and other infections of interest, 17 (0.85%) patients in each treatment group had a serious event. 11 (0.55%) of 2002 patients in the belimumab group versus 15 (0.75%) of 2001 in the placebo group had opportunistic infections (sponsor adjudicated), of which eight were serious (six [0.30%] vs two [0.1%]; appendix p 12).

Figure 2 also shows the differences between groups for non-melanoma skin cancers and other malignancies. Overall, nine (0.45%) of 2002 patients in the belimumab group had malignancies (four solid tumours, one haematological malignancy, and four non-melanoma skin cancers), and eight (0.40%) of 2001 patients did in the placebo group (five solid tumours, three non-melanoma skin cancers).

A higher incidence of on-treatment serious infusion and hypersensitivity reactions, occurring within 3 days of the infusion date, was reported with belimumab than with placebo (figure 2). Eight (0.40%) of 2002 patients in the belimumab group versus two (0.10%) of 2001 in the placebo group reported at least one event (difference 0.30%, 95% CI –0.01 to 0.61). The appendix summarises different hypersensitivity reactions (p 13).

More belimumab-treated patients had serious depression than did those treated with placebo (seven [0.35%] of 2002 vs one [0.05%] of 2001; difference 0.30%, 95% CI 0.02 to 0.58; figure 2). Treatment-emergent suicidality was reported for 28 (1.42%) of 1972 patients in the belimumab group and 23 (1.16%) of 1986 in the placebo group (difference 0.26%, 95% CI –0.44 to 0.96; figure 2).

During the on-treatment period, overall incidences of PSAP-defined depression, suicide, or self-injury events were greater in the belimumab group (18 [0.90%] of 2002



**Figure 2: On-treatment deaths and protocol-defined AEs**

For the as-treated population, the on-treatment period was defined as the period between first dose and last dose, plus 28 days (or death). AEsI=adverse event of special interest. C-SSRS=Columbia-Suicide Severity Rating Scale. MedDRA=Medical Dictionary for Regulatory Activities. NMSC=non-melanoma skin cancer. \*Depression serious adverse events (including serious mood disorders and anxiety) per customised MedDRA queries (MedDRA version 21.1). †Per anaphylactic reaction broad search customised MedDRA queries (MedDRA version 21.1), occurring on or within 3 days of infusion date. ‡Treatment-emergent suicidal ideation or behaviour. Patients must have at least one on-treatment C-SSRS and a pre-treatment C-SSRS assessment: 1972 did in the belimumab group vs 1986 in the placebo group.

patients) than the placebo group (six [0.30%] of 2001 patients; table 2). More patients in the belimumab group had sponsor-adjudicated serious suicide or self-injury than in the placebo group (15 [0.75%] of 2002 vs five [0.25%] of 2001; difference 0.50%, 95% CI 0.06–0.94; table 2). Mean SLE duration, mean baseline SELENA-SLEDAI score, and the proportion of patients with past or current psychiatric disorder were higher among belimumab-treated patients who developed depression or had suicide or self-injury events than among placebo-treated patients who developed these events (appendix p 14), and they were also higher than in the overall patient population recruited for this trial. However, these data are insufficient to derive firm conclusions about a cause and effect relation between medical history, baseline disease activity, and subsequent psychiatric disease course.

On-study incidences of PSAP-defined depression, suicide, or self-injury events were the same as in the on-treatment period (data not shown). During the on-study period, suicidal ideation or behaviour was reported by 48 (2.43%) of 1974 patients in the belimumab group and 39 (1.96%) of 1988 patients in the placebo group (post hoc, difference 0.47%, 95% CI -0.44 to 1.38; appendix p 15). Of the patients who had a pre-treatment history of suicidal ideation or behaviour, 126 (85.71%) of 147 in the belimumab group and 108 (82.44%) of 131 in the placebo group had no ideation or behaviour during the on-study period.

A summary of outcomes and follow-up for patients with on-study, sponsor-adjudicated serious suicide or self-injury events showed that 12 (80%) of 15 events among belimumab-treated patients and five (100%) of five events among placebo-treated patients resolved with no recurrence (appendix p 16). In the belimumab group, one patient had depression, which recovered or resolved with sequelae, and two patients had unresolved depression. Both patients discontinued study treatment: one withdrew

	Belimumab group (n=2002)	Placebo group (n=2001)
Serious depression, suicide, or self-injury*	18 (0.90%)	6 (0.30%)
Serious depression	7 (0.35%)	1 (0.05%)
Difference (95% CI)	0.30% (0.02–0.58)	Ref (–)
Serious suicide or self-injury per SMQ†	11 (0.55%)	5 (0.25%)
Serious suicide or self-injury per sponsor adjudication	15 (0.75%)	5 (0.25%)
Difference (95% CI)‡	0.50% (0.06–0.94)	Ref (–)
Suicidal behaviour per sponsor adjudication	4 (0.20%)	1 (0.05%)
Completed suicide per sponsor adjudication	0	0
Suicidal ideation per sponsor adjudication	10 (0.50%)	3 (0.15%)
Self-injurious behaviour without suicidal intent per sponsor adjudication	1 (0.05%)	1 (0.05%)

Shows adverse events of special interest with events as defined in the programme safety analysis plan, and including events in the on-treatment period (the period between first dose and last dose, plus 28 days, or death) and the on-study period (the period between first dose and the end of week 52 of study follow-up, or death). For the as-treated population. Patients were only counted once per category. There was the same number of patients with depression, suicide, or self-injury during the on-treatment and on-study periods; all events were serious. MedDRA=Medical Dictionary for Regulatory Activities. SMQ=Standardised MedDRA Queries. \*Per customised MedDRA query (MedDRA version 21.1). †MedDRA version 21.1. ‡A post hoc analysis was done for this category because there appeared to be a notable difference in incidence between treatment groups, which was originally not anticipated.

**Table 2: Depression and suicide or self-injury**

from the study at the time of the event, and the other was lost to follow-up approximately 6 weeks later. No suicide-related deaths were reported.

242 (12.09%) of 2002 patients in the belimumab group and 256 (12.79%) of 2001 in the placebo group had on-treatment AEsI or serious adverse events (table 3). 65 (3.25%) patients in the belimumab group discontinued treatment due to these events versus 61 (3.05%) in the placebo group. The most common reason for discontinuation in each group was infections and infestations (22 [1.10%] of 2002 in the belimumab group vs 23 [1.15%] of 2001 in the placebo group).

Efficacy endpoints are summarised in the appendix (p 17). Among patients with baseline corticosteroid doses of

	Belimumab group (n=2002)	Placebo group (n=2001)
Any event	242 (12.09%)	256 (12.79%)
Infections and infestations	93 (4.65%)	118 (5.90%)
Gastrointestinal disorders	18 (0.90%)	19 (0.95%)
Musculoskeletal and connective tissue disorders	9 (0.45%)	24 (1.20%)
Blood and lymphatic system disorders	12 (0.60%)	18 (0.90%)
Nervous system disorders	14 (0.70%)	16 (0.80%)
Cardiac disorders	16 (0.80%)	12 (0.60%)
Respiratory, thoracic, and mediastinal disorders	9 (0.45%)	19 (0.95%)
Renal and urinary disorders	11 (0.55%)	16 (0.80%)
Psychiatric disorders	20 (1.00%)	6 (0.30%)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	12 (0.60%)	13 (0.65%)
Injury, poisoning, and procedural complications	14 (0.70%)	8 (0.40%)
Reproductive system and breast disorders	8 (0.40%)	11 (0.55%)
Skin and subcutaneous tissue disorders	11 (0.55%)	8 (0.40%)
General disorders and administration site conditions	5 (0.25%)	10 (0.50%)
Vascular disorders	10 (0.50%)	4 (0.20%)
Hepatobiliary disorders	5 (0.25%)	8 (0.40%)
Immune system disorders	7 (0.35%)	3 (0.15%)

Data are n (%). Shows adverse events of special interest and serious adverse events occurring in more than four patients in either treatment arm for the on-treatment period (in the as-treated population). The on-treatment period was defined as the period between first dose and last dose, plus 28 days (or death). Patients counted only once per system organ class.

**Table 3: Adverse events by system organ class**

more than 7.5 mg per day, 196 (19.88%) of 986 in the belimumab group and 160 (16.16%) of 990 in the placebo group had a reduction of at least 25% to 7.5 mg per day or lower during weeks 40–52 (odds ratio 1.30, 95% CI 1.03–1.65;  $p=0.028$ ). At week 52, among patients who completed treatment with an assessment at both baseline and week 52, 45 (2.76%) of 1630 patients in the belimumab group and 52 (3.19%) of 1631 in the placebo group had worsening SDI (observed change  $>0$ ) compared with baseline (OR 0.87, 95% CI 0.58–1.31;  $p=0.50$ ). Also, 830 (50.15%) of 1655 who completed treatment in the belimumab group versus 813 (49.39%) of 1646 in the placebo group were on immunomodulatory medication for SLE at baseline, and 808 (48.82%) versus 810 (49.21%) were on these medications at treatment completion.

The percentage of patients admitted to hospital was similar for the belimumab and placebo groups (208 [10.39%] of 2001 vs 221 [11.04%] of 2002; appendix p 17). Of patients admitted to hospital, most patients in both groups were admitted to hospital only once (170 [81.73%] of 208 vs 175 [79.19%] of 221). Only six (0.30%) of 2001 patients in the belimumab group and four (0.20%) of 2002 in the placebo group were admitted to hospital more than three times.

## Discussion

Overall, the on-treatment incidences of all-cause mortality and most AESIs, including serious infections, opportunistic infections or other infections of interest, and all

malignancies, were similar between patients treated for SLE with intravenous belimumab and those given placebo. This study represents the largest controlled clinical study of SLE to date. The use of standard therapies for SLE was not restricted in either treatment group; this arrangement was especially pertinent for patients who were assigned to placebo, because it ensured that they were still able to receive treatment for SLE.

The overall incidence of on-treatment, 1-year mortality in our study (0.5%) was consistent with the incidences of 0.4–1% reported in previous 52–76-week randomised controlled trials of belimumab.<sup>4,5,10,11</sup> The on-treatment follow-up adjusted mortality rate was 0.55 per 100 person-years. In the general population of patients with SLE, including those with CNS disease or active lupus nephritis, the rate of mortality is 1.63 per 100 person-years.<sup>12</sup> Our mortality results had a precision of  $\pm 0.41\%$  around the treatment difference, which was better than the planned  $\pm 0.46\%$  precision. Unlike the previous trials, the BASE trial did not set eligibility criteria based on SLE disease activity level—ie, no requirement for a minimum SELENA-SLEDAI score at screening or restrictive SLE medication use before the study—nor did it exclude patients because of psychiatric history; therefore, the study population is more reflective of clinical practice than previous randomised trials.

Although the absolute number of events was low, the incidence of infection-related deaths was higher with belimumab compared with placebo, as reported in phase 3 studies of belimumab.<sup>5,10</sup> Overall, hospital admission for infections are more common in patients with SLE than in the general population,<sup>13</sup> probably a reflection of the use of corticosteroids and immunosuppressants as standard therapy,<sup>14</sup> and patients living with more comorbidities and organ damage as they age.<sup>15,16</sup> Overall, the data suggest that patients are not more likely to have a serious infection with belimumab, but may have an increased risk of a fatal infection if a serious infection occurs. Therefore, it is important to monitor patients with SLE for risk of infections and to manage infections appropriately when patients receive belimumab treatment in combination with standard therapy.

Serious infusion and hypersensitivity reactions were more common with belimumab than placebo, but there was a low absolute number of events in each group. Serious hypersensitivity reactions to intravenous biological drugs are not uncommon and have been reported with similar rates to that reported for belimumab—eg, with trastuzumab (0.5%) and tocilizumab (0.1–0.7%).<sup>17</sup>

Because of the significant disease burden, depression and psychiatric issues such as suicidality have a higher incidence in patients with SLE than in the general population.<sup>18,19</sup> This effect probably contributed to the incidence of psychiatric events in our study. A higher incidence of serious depression and serious suicidality events was recorded in the belimumab group than with placebo, although the absolute number of events was low.

Suicidality was measured by standardised C-SSRS and general serious adverse event reporting, both of which showed similar results, although the treatment difference using C-SSRS was smaller. Most sponsor-adjudicated, on-study serious suicide or self-injury events resolved, including events among the belimumab-treated patients who continued treatment after event onset. Additionally, there were no recurrent events and no suicidal deaths. No clear explanatory mechanism of action exists for the observation of increased suicide or self-injury events with belimumab treatment, although a link between reductions in BAFF, which might support neural cell survival, and altered neural function and mental state has been suggested.<sup>20,21</sup> However, the relevance of those preliminary data to SLE is unclear. Physicians and patients should be keenly aware of the need for close management of psychiatric issues in patients with SLE, including those receiving belimumab treatment.

In addition to examining the safety of belimumab, we also assessed several measures of efficacy. We found a statistically significant increase in the proportion of patients deemed corticosteroid responders in the belimumab group compared with the placebo group, supporting a steroid-sparing effect of belimumab.<sup>22–24</sup> Although the difference between belimumab and placebo was similar to that reported in phase 3 studies,<sup>3–5,10,22</sup> the effect size was small. There were differences in our study's design compared with previous belimumab studies measuring steroid-sparing effects,<sup>3–5,10</sup> including no protocol-mandated corticosteroid taper or assessment of change in disease activity or efficacy. Over the 12 months of the BASE study, we recorded no clinically relevant change in the use of immunomodulatory agents by patients in the placebo group. Considering this observation alongside the inclusion criteria of the study, it is possible that many of the patients in this study had stable disease that did not, by itself, require additional therapy. Therefore, for patients with SLE who do require additional therapy, the findings of BASE further support the idea that belimumab is a well tolerated medication with proven efficacy, and that its use in combination with existing therapy for SLE has few significant additional risks.

We found that the rate of organ damage accrual was slightly higher in patients who completed treatment in the placebo group than in the belimumab group, largely consistent with trends in previous 52-week trials.<sup>5,10</sup> A longer-term study by Urowitz and colleagues,<sup>25</sup> using a propensity score-matched comparative analysis, found that after 5 years of treatment, belimumab had significantly reduced organ damage accrual compared with placebo.

Limitations of the BASE study included the 52-week duration of follow-up, whereas in clinical practice, treatment can continue for more than 1 year, particularly in patients who respond to belimumab treatment. However, our study complements an open-label study, which lacked a placebo control but followed up patients for 7 years of treatment, and showed stable or decreased

incidence of adverse events and sustained efficacy for belimumab with long-term exposure.<sup>26</sup> Second, although C-SSRS has been validated, it could potentially miss some suicidal ideation or behaviour.<sup>24</sup> However, in this study, the C-SSRS was used in conjunction with serious adverse event data collection to assess suicidality. Furthermore, due to eligibility criteria, such as those excluding the most severe patients (eg, with lupus nephritis or CNS lupus), the patient population in this study might not have been fully representative of the general population of patients with SLE, meaning that the incidence of some AESIs might be higher in a general SLE population. Nevertheless, the generalisability of BASE should be greater than that of smaller single-centre studies. The standard therapy for SLE varied across the countries and study centres of BASE; however, the randomised design of the study should have mitigated any resulting bias.

In conclusion, the results of this study suggest that the incidences of mortality and of most AESIs including serious infections, opportunistic infections and other infections of interest, and all malignancies are similar between belimumab and placebo, with a higher incidence of fatal infections, serious infusion and hypersensitivity reactions, serious depression, and serious suicidal ideation or behaviour and self-injury events with belimumab versus placebo. These findings are consistent with smaller studies.<sup>4,5,10,11</sup> This higher incidence with belimumab versus placebo of AESIs that could lead to severe adverse outcomes, such as fatal infections, serious suicidal ideation or behaviour and self-injury events, underscores the need for close follow-up and prompt management by patients and physicians to ensure that patients with SLE achieve the clinical benefits of belimumab with minimal adverse events.

#### Contributors

DLB designed the study, and collected, analysed, and interpreted data. SZS, MAS, JC-CW, DT, WS, RAdT, TM, MRAB, KM-M, CA-M, SN, MG, IG-DLT, JOR, RAL, JRT, RP, AN, AP, and KST collected, analysed, and interpreted data. DAR designed the study and analysed and interpreted data. JH analysed and interpreted data. BJ interpreted data.

#### Declaration of interests

RAL, DLB, RP, JH, BJ, and DAR are employees of GSK and hold stocks and shares in the company. JRT and KST were GSK employees at the time of the study and hold stocks and shares in the company. JC-CW has received research funding and honoraria from TSH BioPharm, AbbVie, BMS, Celgene, Janssen, Novartis, Pfizer, and UCB Pharma; and honoraria from Chugai, Eisai, and Sanofi-Aventis. SZS has received consulting fees from GSK and research funding from Pfizer. WS has received research funding from GSK and consulting fees from Janssen R&D. RAdT has received research funding from GSK, AbbVie, Novartis, and Pfizer; consulting fees from AbbVie, Novartis, UCB, and Janssen; and honoraria from AbbVie, Novartis, UCB, Janssen, and Apsen. TM has received research funding from GSK, Janssen, Roche, Eli Lilly, and Amgen; consulting fees from Janssen, UCB, and Novartis; and honoraria from Janssen, Roche, Pfizer, Novartis, and AbbVie. KM-M has received consulting fees from ChemoCentryx and clinical trial funding from AstraZeneca, Gilead, GSK, and Merck. CA-M has received consulting fees and honoraria from Pfizer, Eli Lilly, and Takeda. SN has received honoraria from Novartis, Pfizer, Abbott, Johnson & Johnson, GSK, and Astellas. JOR has received consulting fees from GSK. AP is an employee of ViiV



Healthcare, was an employee of ViiV Healthcare at the time of the study, and owns stocks and shares in GSK. AN, DT, IG-DLT, MRAB, MAS, and MG declare no competing interests.

#### Data sharing

Within 6 months of publication, the study will be listed on [www.clinicalstudydatarequest.com](http://www.clinicalstudydatarequest.com), where requests for anonymised individual patient data and study documents can be made.

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