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ORIGINAL RESEARCH

# Efficacy and safety of belimumab in paediatric and adult patients with systemic lupus erythematosus: an across-study comparison

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## ABSTRACT

**Objective** To assess the efficacy and safety of belimumab in paediatric versus adult patients with systemic lupus erythematosus (SLE).

**Methods** We performed across-study comparisons of patients with active SLE who received belimumab or placebo, plus standard therapy, in PLUTO (paediatric phase II) and BLISS-52, BLISS-76, BLISS-NEA and EMBRACE (adult phase III). Analysed efficacy data included Week 52 SLE Responder Index (SRI)-4 response rate (EMBRACE: SRI with modified Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) proteinuria scoring (SRI-S2K)); SRI-4 response rate (EMBRACE: SRI-S2K) according to baseline disease activity indicators (Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score; anti-dsDNA/C3/C4 levels); Week 52 SRI-6 response rate; and time to first severe flare (SELENA-SLEDAI Flare Index) over 52 weeks. Safety data were compared for all aforementioned studies along with adult LBSL02 (phase II) and BLISS-SC (phase III).

**Results** SRI-4 response rates were similar across the paediatric and adult studies; more belimumab-treated patients achieved SRI-4 responses versus placebo (PLUTO: 52.8% vs 43.6%; BLISS-52: 57.6% vs 43.6%; BLISS-76: 43.2% vs 33.8%; BLISS-NEA: 53.8% vs 40.1%; EMBRACE: 48.7% vs 41.6%). Across all studies, SRI-4 response rates were generally greater in patients with baseline SELENA-SLEDAI scores ≥10 than in patients with baseline SELENA-SLEDAI scores ≤9. A similar proportion of belimumab-treated patients achieved SRI-6 across all studies (PLUTO: 41.2%; BLISS-52: 46.2%; BLISS-76: 33.1%; BLISS-NEA: 43.9%; EMBRACE: 37.5%). Belimumab reduced the risk of severe flare versus placebo in all studies. The incidence of adverse events was similar across all studies.

**Conclusions** These analyses demonstrate consistent efficacy and safety of belimumab plus standard therapy across paediatric and adult patients with SLE.

**Trial registration numbers** PLUTO (NCT01649765); BLISS-52 (NCT00424476); BLISS-76 (NCT00410384);

## Key messages

**What is already known about this subject?**
► Paediatric patients with childhood-onset systemic lupus erythematosus (cSLE) exhibit higher disease activity and faster damage accrual over time compared with those diagnosed in adulthood.
► Belimumab specifically inhibits human B-lymphocyte stimulator protein/B cell-activating factor and has been studied for the treatment of SLE in adults and children ≥5 years of age.

**What does this study add?**
► This across-study comparison demonstrated consistent efficacy and safety of belimumab plus standard therapy in paediatric patients with cSLE and adult patients with SLE across multiple endpoints, with generally higher SLE Responder Index-4 responses in patients treated with intravenous belimumab than with placebo.

**How might this impact on clinical practice or further developments?**
► The current across-study comparison provides evidence that the efficacy and safety of belimumab in paediatric patients with SLE are comparable with that observed in adult populations.

BLISS-NEA (NCT01345253); EMBRACE (NCT01632241); BLISS-SC (NCT01484496); and LBSL02 (NCT00071487).

## INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic, multisystem autoimmune disease characterised by autoantibody production and abnormal B cell function as well as marked clinical heterogeneity.[1][2] The disease often follows a relapsing and

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remitting course marked by intermittent flares.[3 4] Treatment strategies aim to achieve remission or low disease activity and prevent flares in all organs, using the lowest possible dose of glucocorticoids.[5]

Although patients with childhood-onset SLE (cSLE) and adult-onset SLE (aSLE) share many immunogenetic and serological similarities, some differences are recognised,[2 6] with several studies showing cSLE to be more severe than aSLE, with higher disease activity and greater risk of renal and neurological involvement.[7–11] Furthermore, cSLE has been associated with a twofold to threefold higher risk of mortality compared with aSLE.[11 12] Like aSLE, paediatric patients with cSLE are treated using combinations of glucocorticoids, immunosuppressants, antimalarials and non-steroidal anti-inflammatory drugs.[13] Both short-term and long-term management of cSLE are challenging owing to high disease activity as well as the incremental years of disease burden following the early disease onset.

Belimumab is a human monoclonal antibody which specifically inhibits human B-lymphocyte stimulator protein/B cell-activating factor.[14] The efficacy and safety of intravenous and subcutaneous belimumab have been demonstrated in several phase III studies of adults with active, autoantibody-positive SLE receiving standard therapy.[15–19] The efficacy and safety of intravenous belimumab were also demonstrated in children 5–17 years of age with SLE in the PLUTO study.[20] Belimumab is approved for the treatment of patients with active, autoantibody-positive SLE receiving standard therapy, by intravenous administration in patients ≥5 years of age and subcutaneous administration in adults.[21 22] Additionally, intravenous and subcutaneous belimumab were approved for the treatment of adult patients with active lupus nephritis receiving standard therapy based on the results of the phase III, double-blind, placebo-controlled BLISS-LN study (BEL114054; NCT01639339).[21 23 24]

In the present analyses, we performed across-study comparisons to assess the efficacy and safety of belimumab in paediatric versus adult patients with SLE.

## METHODS
### Study design and patients
This across-study comparison of clinical trials of belimumab considered data from children with SLE participating in the phase II PLUTO study (BEL114055; NCT01649765)[20] and six adult SLE studies: phase III BLISS-52 (BEL110752; NCT00424476)[15]; phase III BLISS-76 (BEL110751; NCT00410384)[17]; phase III BLISS-NEA (BEL113750; NCT01345253)[16]; phase IIIb EMBRACE (BEL115471; NCT01632241)[19]; phase III BLISS-SC (BEL112341; NCT01484496)[18]; and phase II LBSL02 (NCT00071487).[25]

Full details of the methods of these studies have been published previously.[15–20 25] In brief, all studies were randomised, double-blind and placebo-controlled. Doses of belimumab at 1, 4 or 10 mg/kg intravenously and

200 mg subcutaneously were evaluated. Key eligibility criteria for patients were generally similar across studies. All eligible patients continued standard therapy in accordance with national and institutional approaches, but consistent with the study protocol. The double-blind phase was 52 weeks for all studies except for BLISS-76, which was 76 weeks. Further details on the study design and key eligibility criteria of the studies included in the current efficacy comparison are presented in online supplemental table 1.

All patients or patients' parent(s)/legal guardian(s) gave written informed consent.

### Study endpoints and assessments
The primary efficacy endpoint in PLUTO, BLISS-52, BLISS-76 and BLISS-NEA was the SLE Responder Index (SRI)-4 response rate at Week 52, defined as ≥4-point reduction from baseline in the Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score; no worsening (increase of <0.3 points from baseline) in Physician's Global Assessment (PGA; range 0–3; 0=inactive); and no new British Isles Lupus Assessment Group (BILAG) A or no two new BILAG B organ domain scores compared with baseline. In EMBRACE, the primary endpoint was SRI at Week 52, but with modified SLEDAI-S2K scoring for proteinuria (SRI-S2K). The SELENA-S2K proteinuria rule scores 4 points for proteinuria >0.5 g/24 hours at any time and brings the disease activity scale into alignment with other items in the SELENA-SLEDAI scale, where points are assigned if a manifestation is present and points removed only if the manifestation completely resolves (in the unmodified SELENA-SLEDAI scale, 4 points are scored for new onset or recent increase in proteinuria >0.5 g/24 hours).

Other endpoints reported in these studies were the following: (1) SRI-4 response (SRI-S2K for EMBRACE) according to baseline disease activity indicators (SELENA-SLEDAI score, anti-dsDNA and complement C3/C4 levels); (2) SRI-6 response at Week 52, defined in the same way as SRI-4 except for the use of a higher threshold for improvement in SELENA-SLEDAI of ≥6 (calculated post-hoc in BLISS-52 and BLISS-76 and using SRI-S2K ≥6-point reduction in EMBRACE); (3) time to first severe flare over 52 weeks, evaluated using the modified SELENA-SLEDAI Flare Index (SFI; also see online supplemental materials)[26]; and (4) adjusted mean change from baseline in average daily prednisone dose and proportion of patients with average prednisone dose reduction ≥25% from baseline to ≤7.5 mg/day (a clinically meaningful reduction) during Weeks 40–52 among those receiving ≥7.5 mg prednisone at baseline, or ≥25% from baseline during Weeks 44–52 among patients taking prednisone (PLUTO only).

Herein, outputs from the above efficacy endpoints were compared across the included studies. SRI results described in the following section refer to the composite outcome using either SELENA-SLEDAI or SELENA-S2K scoring.

**Table 1** Baseline demographic and clinical characteristics of the studies included in the efficacy comparison (mITT population)

| | PLUTO[20] | | BLISS-52[15] | | BLISS-76[17] | | BLISS-NEA[16] | | EMBRACE[19] | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Placebo (n=40) | Belimumab 10mg/kg intravenously (n=53) | Placebo (n=287) | Belimumab 10mg/kg intravenously (n=290) | Placebo (n=275) | Belimumab 10mg/kg intravenously (n=273) | Placebo (n=226) | Belimumab 10mg/kg intravenously (n=451) | Placebo (n=149) | Belimumab 10mg/kg intravenously (n=299) |
| Age, years, mean (SD) | 14.8 (2.2) | 13.5 (2.6) | 36.2 (11.8) | 35.4 (10.8) | 40.0 (11.9) | 40.5 (11.1) | 31.7 (9.2) | 32.3 (9.7) | 39.3 (12.2) | 38.6 (11.1) |
| Female, n (%) | 39 (97.5) | 49 (92.5) | 270 (94.1) | 280 (96.6) | 252 (91.6) | 259 (94.9) | 210 (92.9) | 419 (92.9) | 144 (96.6) | 290 (97.0) |
| **Race*, n (%)** | | | | | | | | | | |
| White | 21 (52.5) | 27 (50.9) | 82 (28.6) | 71 (24.5) | 188 (68.4) | 189 (69.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Native American from North/Central/South America or Alaskan Native† | 11 (27.5) | 15 (28.3) | 89 (31.0) | 92 (31.7) | 36 (13.1) | 34 (12.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Asian | 6 (15.0) | 8 (15.1) | 105 (36.6) | 116 (40.0) | 11 (4.0) | 11 (4.0) | 226 (100.0) | 451 (100.0) | 0 (0.0) | 0 (0.0) |
| Black African/American ancestry | 2 (5.0) | 3 (5.7) | 11 (3.8) | 11 (3.8) | 39 (14.2) | 39 (14.3) | 0 (0.0) | 0 (0.0) | 143 (96.0) | 293 (98.0) |
| Native Hawaiian or other Pacific Islander | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Multiracial | 0 (0.0) | 0 (0.0) | 1 (0.3) | 1 (0.3) | 2 (0.7) | 3 (1.1) | 0 (0.0) | 0 (0.0) | 6 (4.0) | 6 (2.0) |
| **Ethnicity, n (%)** | | | | | | | | | | |
| Hispanic or Latino | 17 (42.5) | 26 (49.1) | 143 (49.8) | 136 (46.9) | 55 (20.0) | 56 (20.5) | 1 (0.4) | 1 (0.2) | 73 (49.0) | 142 (47.5) |
| Non-Hispanic or non-Latino | 23 (57.5) | 27 (50.9) | 144 (50.2) | 154 (53.1) | 220 (80.0) | 217 (79.5) | 225 (99.6) | 450 (99.8) | 76 (51.0) | 157 (52.5) |
| SLE disease duration, years, mean (SD) | 2.7 (1.8) | 2.2 (2.0) | 5.9 (6.2) | 5.0 (5.1) | 7.4 (6.7) | 7.2 (7.5) | 6.0 (5.2) | 6.1 (5.0) | 6.9 (7.4) | 7.3 (7.1)‡ |
| SELENA-SLEDAI score, mean (SD) | 10.4 (3.6)§ | 10.3 (3.3) | 9.7 (3.6) | 10.0 (3.9) | 9.8 (4.0) | 9.5 (3.6) | 10.2 (4.1) | 9.8 (3.8) | 10.2 (2.9) | 9.9 (3.5) |
| Physician's Global Assessment, mean (SD) | 1.4 (0.4) | 1.3 (0.4) | 1.4 (0.5) | 1.4 (0.5) | 1.5 (0.5) | 1.4 (0.5) | 1.6 (0.4)¶ | 1.6 (0.5)** | 1.5 (0.4) | 1.5 (0.5) |
| BILAG 1A or 2B, n (%) | 29 (72.5) | 37 (69.8) | 166 (57.8) | 172 (59.3) | 187 (68.0) | 160 (58.6) | 108 (47.8) | 204 (45.2) | 107 (71.8) | 215 (71.9) |
| Proteinuria, g/24 hours, mean (SD) | 0.5 (1.1) | 0.2 (0.2) | 0.6 (1.2) | 0.5 (0.9) | 0.4 (0.8) | 0.4 (0.7) | 1.0 (1.4) | 1.0 (1.3) | 0.6 (1.1) | 0.4 (0.9) |

*Patients who checked more than one race category were counted under individual race category according to the minority rule as well as the multiracial category.
†Included patients having origins in any of the original peoples of North and South America (including Central America) and who maintain tribal affiliation or community attachment.
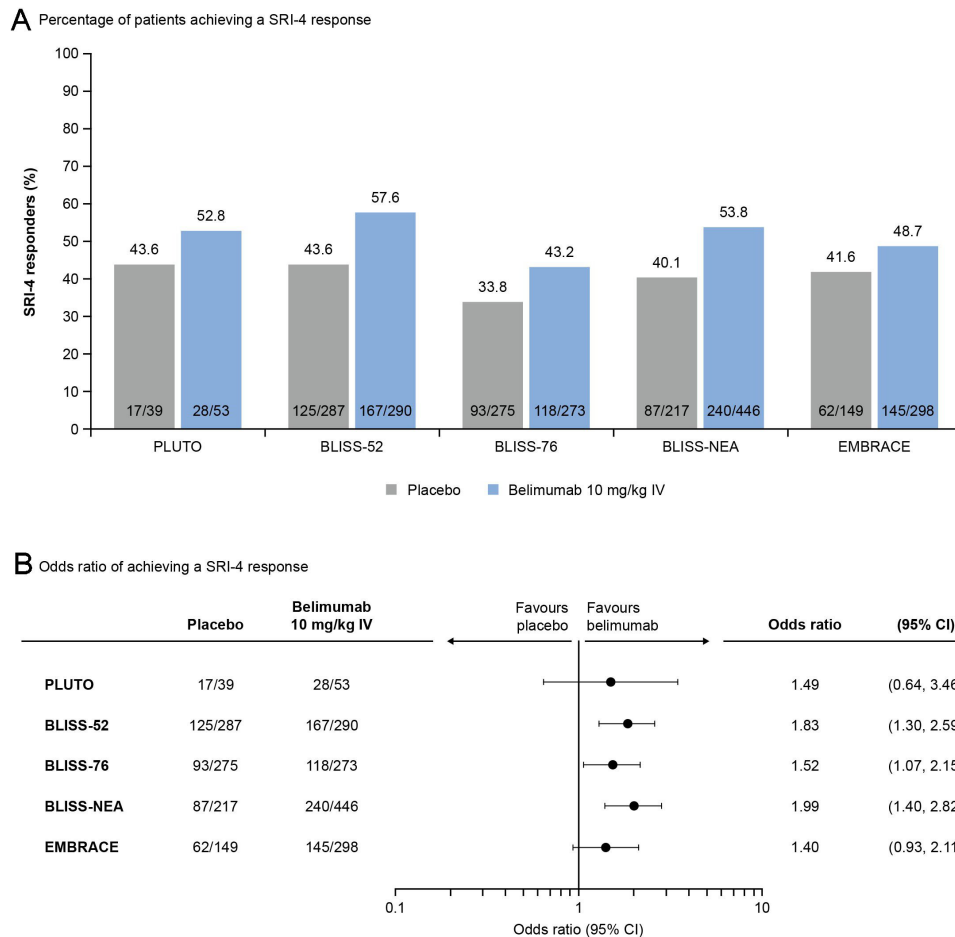‡n=298.
§n=39.
¶n=225.
**n=450.
BILAG, British Isles Lupus Assessment Group; mITT, modified intention-to-treat; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index; SLE, systemic lupus erythematosus.

**A** Percentage of patients achieving a SRI-4 response



**B** Odds ratio of achieving a SRI-4 response



**Figure 1** SRI-4 response with belimumab and placebo at Week 52 in the cSLE PLUTO study and aSLE phase III studies (mITT populations). Note: SRI-4 response rate assessed using SRI-S2K in EMBRACE. Patients without a complete baseline assessment were excluded from the analysis; patients with a baseline SELENA-SLEDAI score of <4 were excluded as they had no opportunity to meet the responder definition. OR for response rate: belimumab/placebo. aSLE, adult-onset systemic lupus erythematosus; cSLE, childhood-onset systemic lupus erythematosus; IV, intravenous; mITT, modified intention-to-treat; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index; SLE, systemic lupus erythematosus; SRI, SLE Responder Index; SRI-S2K, SRI with modified SLEDAI proteinuria scoring.

Data from the LBSL02 study were excluded from the comparison of efficacy due to differences in treatment failure rules, efficacy endpoints and eligibility criteria. Given that the subcutaneous formulation of belimumab is not approved for paediatric use, data from the BLISS-SC study were omitted in the comparison of efficacy outcomes. However, patients from the LBSL02 and BLISS-SC studies were included in the safety comparisons. In BLISS-NEA and EMBRACE, safety analyses were performed on the safety population that comprised all randomised patients who were treated with at least one dose of study treatment.

The frequency of adverse events (AEs), treatment-related AEs, serious adverse events (SAEs), AEs resulting in study agent discontinuation, deaths and AEs of special interest (AESI) over 52 weeks was numerically compared across all studies. AESI included malignancies, infections, postinjection/infusion systemic reactions and depression/suicide/self-injury.

## Data analyses

No formal statistical comparisons were conducted, and all across-study efficacy and safety comparisons are descriptive in nature only.

In PLUTO, BLISS-52, BLISS-76, LBSL02 and BLISS-SC, all analyses were performed on the modified intention-to-treat (mITT) population, defined as all patients who were randomised and received at least one dose of study treatment.[15–20 25] In BLISS-NEA and EMBRACE, safety analyses were performed on the safety population that comprised all randomised patients who were treated with at least one dose of study treatment. Efficacy was assessed on the mITT population, which comprised the safety population but with some patients excluded due to non-compliance.[16 19] The SRI-4 and SRI-6 analyses were conducted on the mITT population, including only the patients with baseline SELENA-SLEDAI scores ≥4 and ≥6. Patients with missing SRI components at baseline were excluded from SRI analysis. For the comparison of the SRI-4 response according to baseline disease activity,

A Percentage of patients achieving a SRI-6 response
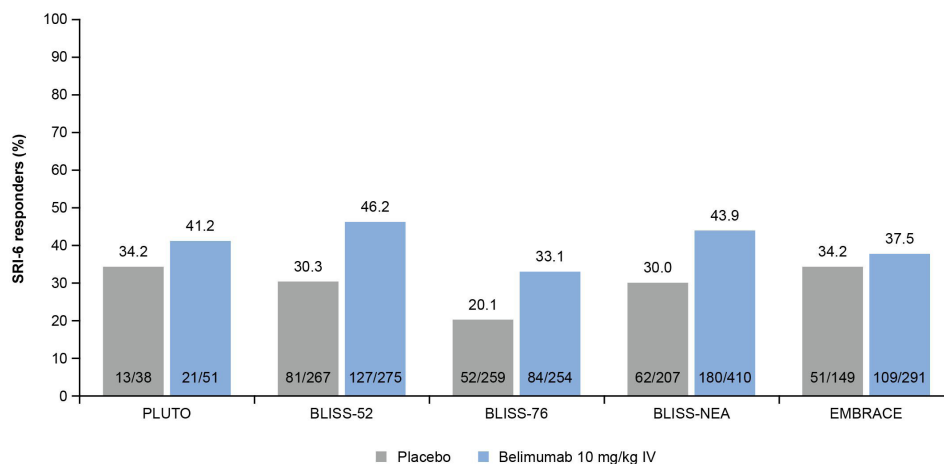
B Odds ratio of achieving a SRI-6 response
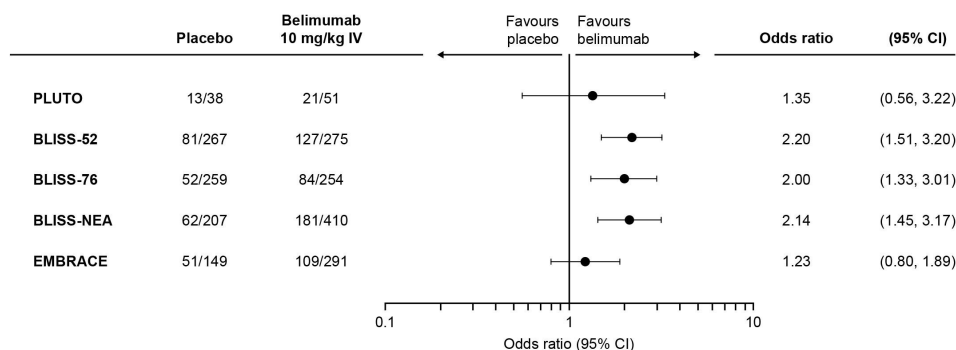
**Figure 2** (A) Percentage of patients achieving a SRI-6 response and (B) odds ratio of achieving a SRI-6 response at Week 52 in the cSLE PLUTO and aSLE phase III studies (mITT population). Note: SRI-6 response rate assessed using SRI-S2K in EMBRACE. Patients with a baseline SELENA-SLEDAI score of <6 were excluded as they had no opportunity to meet the responder definition. OR for response rate: belimumab/placebo. aSLE, adult-onset systemic lupus erythematosus; cSLE, childhood-onset systemic lupus erythematosus; IV, intravenous; mITT, modified intention-to-treat; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index; SLE, systemic lupus erythematosus; SRI, SLE Responder Index; SRI-S2K, SRI with modified SLEDAI proteinuria scoring.

BLISS-52 and BLISS-76 data were pooled in a post-hoc analysis, as described previously,[27] and compared descriptively with data from the other studies. The efficacy comparison was based only on data from patients who received belimumab 10 mg/kg intravenously. The forest plots, which visually compare SRI responses, show the OR and 95% CI versus placebo from logistic regression analysis adjusted for relevant differences in baseline characteristics between randomisation groups (online supplemental materials). In the SFI flare analysis, the HR and 95% CI were calculated using Cox proportional hazard models adjusted using the same covariates as the SRI response analysis. The proportion of patients with average prednisone dose reduction ≥25% from baseline to ≤7.5 mg/day at Weeks 40–52 among those receiving ≥7.5 mg prednisone at baseline, or ≥25% from baseline at Weeks 44–52 among patients taking prednisone (PLUTO only), was also based on logistic regression models adjusted for the same covariates as for SRI response analysis, with the addition of baseline prednisone use.

For safety analyses in the adult population, data from a previous pooled analysis of LBSL02, BLISS-52, BLISS-76, BLISS-NEA, EMBRACE and BLISS-SC are reported here and include all patients who received belimumab 1, 4 or 10 mg/kg intravenously and belimumab 200 mg subcutaneously. Safety data from the adult studies were descriptively compared with the data from paediatric patients of the PLUTO study.
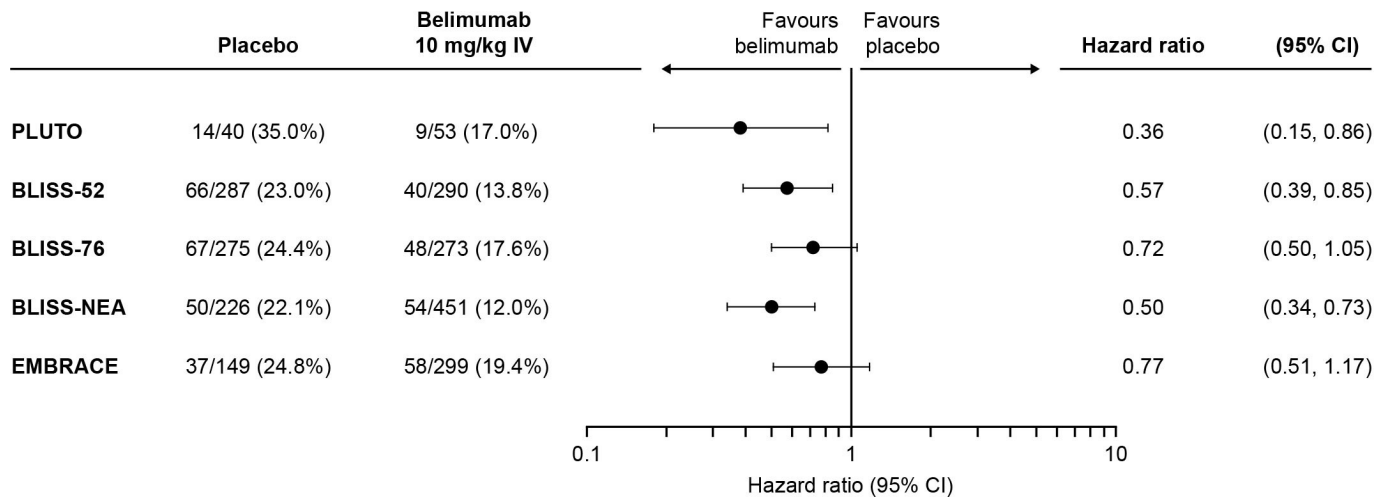
### Patient and public involvement
This study did not involve patients or the public in the design or implementation of the study or the dissemination of its results.

## RESULTS
### Study population
The efficacy analysis (mITT population) of the compared trials included 93 paediatric patients (belimumab 10 mg/

**Figure 3** Proportion of patients with severe flare and reduction in the risk of severe flare over 52 weeks with belimumab versus placebo in the cSLE PLUTO and aSLE phase III studies (mITT populations). HR for rate of severe flare: belimumab/placebo. aSLE, adult-onset systemic lupus erythematosus; cSLE, childhood-onset systemic lupus erythematosus; IV, intravenous; mITT, modified intention-to-treat.

kg intravenously, n=53; placebo, n=40) from the PLUTO study and 2250 adult patients (belimumab 10 mg/kg intravenously, n=1313; placebo, n=937) from the phase III studies. The safety analysis included the same number of patients from PLUTO and 4170 patients (belimumab 1, 4 and 10 mg/kg intravenously and 200 mg subcutaneously, n=2815; placebo, n=1355) from the adult studies. The median duration of exposure was similar across treatment groups and studies, ranging from 364.0 to 392.0 days. The LBSL02 study had only mean values available and the mean duration of exposure was 320.9 days for all active treatments and 328.3 days for placebo.

Most patients (>90%) were female (table 1), and the average disease duration was shorter in the paediatric study compared with the adult studies. SELENA-SLEDAI and PGA scores were similar across studies. The proportion of patients with BILAG 1A or 2B domain score varied across studies, but was consistent within studies for belimumab and placebo groups (table 1).

### Efficacy comparisons

More patients achieved SRI-4 responses with belimumab 10 mg/kg intravenously compared with placebo at Week 52 (figure 1A). In PLUTO, 28 of 53 (52.8%) children achieved SRI-4 response with belimumab, consistent with the results from the adult studies (range: 43.2%–57.6%) (figure 1A). Across all studies, SRI-4 response rates numerically favoured belimumab versus placebo at Week 52 (figure 1B).

In the analysis of SRI-4 response according to baseline disease activity indicators, SRI-4 response rates were higher with belimumab than placebo in most subgroups (online supplemental table 2). Across all adult studies, a higher proportion (OR, 95% CI) of patients with baseline SELENA-SLEDAI scores of ≥10 achieved SRI-4 response compared with patients with baseline SELENA-SLEDAI scores of ≤9 (online supplemental table 2). This

was different in the paediatric study, where the SRI-4 responses (OR, 95% CI) were the same in both subgroups (online supplemental table 2). The SRI-4 responses (OR, 95% CI) were greater with belimumab versus placebo in patients with baseline low C3/C4 and anti-dsDNA ≥30 IU/mL than in patients with baseline normal/high C3/C4 and anti-dsDNA <30 IU/mL across adult studies, but in paediatric patients SRI-4 responses were greater with belimumab versus placebo for patients with baseline normal/high C3/C4 and anti-dsDNA <30 IU/mL (online supplemental table 2).

SRI-6 response rates at Week 52 followed similar patterns to the SRI-4, with more patients in the belimumab group achieving SRI-6 responses at Week 52 compared with placebo across all studies. The proportion of children achieving SRI-6 response with belimumab was 21 out of 51 (41.2%), similar to the results of the adult studies (figure 2A). Similar to the SRI-4 results, SRI-6 response rates favoured belimumab versus placebo at Week 52 across all studies (figure 2B).

The proportion of patients having a severe SFI flare was lower with belimumab versus placebo; in PLUTO, severe flares occurred in 9 of 53 (17%) children receiving belimumab compared with 14 of 40 (35%) receiving placebo, corresponding to a 64% lower risk of severe flares with belimumab (HR: 0.36). In the aSLE studies, the risk of severe flares was also reduced with belimumab, with a reduction rate of 23%–50% (figure 3).

In aSLE studies, among patients with baseline prednisone dose >7.5 mg/day, the proportion of patients who achieved a meaningful reduction of prednisone use during Weeks 40–52 or Weeks 44–52 (PLUTO only) was numerically higher in the belimumab group compared with the placebo group (table 2); this was not the case in the paediatric study, where there was no difference in the frequency of prednisone reduction between the

**Table 2** Reduction in prednisone-equivalent dose by ≥25% from baseline in PLUTO during Weeks 44–52 and by ≥25% from baseline to ≤7.5 mg/day in BLISS-52, BLISS-76, BLISS-NEA and EMBRACE during Weeks 40–52 (mITT population)*

| | PLUTO | | BLISS-52 | | BLISS-76 | | BLISS-NEA | | EMBRACE | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Placebo (n=40) | Belimumab 10 mg/kg intravenously (n=53) | Placebo (n=287) | Belimumab 10 mg/kg intravenously (n=290) | Placebo (n=275) | Belimumab 10 mg/kg intravenously (n=273) | Placebo (n=226) | Belimumab 10 mg/kg intravenously (n=451) | Placebo (n=149) | Belimumab 10 mg/kg intravenously (n=299) |
| Number of patients on prednisone-equivalent dose at baseline | 38 | 50 | 192 | 204 | 126 | 120 | 184 | 352 | 95 | 184 |
| Number (%) of patients with dose reduction | 8 (21.1) | 10 (20.0) | 23 (12.0) | 38 (18.6) | 16 (12.7) | 20 (16.7) | 20 (10.9) | 55 (15.6) | 12 (12.6) | 27 (14.7) |
| OR (95% CI) belimumab vs placebo | – | 0.92 (0.29 to 2.88) | – | 1.75 (0.99 to 3.08) | – | 1.26 (0.61 to 2.60) | – | 1.68 (0.95 to 2.96) | – | 1.30 (0.61 to 2.80) |

*For the aSLE studies, data include only patients with baseline prednisone dose of >7.5 mg/day and show ≥25% reduction in dose to ≤7.5 mg/day. Average daily dose is considered (ie, the 7-day average dose).
aSLE, adult-onset systemic lupus erythematosus; mITT, modified intention-to-treat.

belimumab and placebo groups (n=10/50 (20.0%) and n=8/38 (21.1%)).

## Safety

A summary of AEs, SAEs and AESI from the double-blind phase of the studies is shown in table 3. The incidence of AEs and treatment-related AEs was similar with belimumab in PLUTO and the pooled aSLE studies. In total, 42 of 53 (79.2%) patients receiving belimumab and 33 of 40 (82.5%) patients receiving placebo had ≥1 AEs in the PLUTO study; corresponding values in the pooled aSLE studies were 2440 of 2815 (86.7%) patients and 1184 of 1355 (87.4%) patients, respectively. For belimumab and placebo, respectively, AEs resulting in study drug discontinuation occurred in 3 of 53 (5.7%) and 5 of 40 (12.5%) patients in PLUTO and 184 of 2815 (6.5%) and 109 of 1355 (8.0%) patients in the aSLE studies. In PLUTO, one child in the placebo group died due to acute pancreatitis; no deaths were reported in the belimumab group. In the pooled aSLE studies, 16 of 2815 (0.6%) patients receiving belimumab and 6 of 1355 (0.4%) receiving placebo died (table 3).

The incidence of AESI in PLUTO was generally similar to that of the pooled aSLE studies, with some exceptions (table 3). In the cSLE study, the infections of special interest (opportunistic infections, herpes zoster, tuberculosis and sepsis) were more frequent in the belimumab group versus the placebo group (belimumab: 13.2%, n=7/53 vs placebo: 7.5%, n=3/40). This is different from the pooled aSLE studies, where a similar frequency of infections of special interest (including herpes zoster) was observed (belimumab: 6.1%, n=173/2815 vs placebo: 7.2%, n=97/1355).

## DISCUSSION

In this across-trial comparison of efficacy (non-integrated) and safety (integrated) results from studies in paediatric and adult patients with SLE, the efficacy and safety of belimumab plus standard therapy were consistent across all studies.

Although the SRI was developed for use in adults with SLE, a prospective study has shown SRI-4 and SRI-6 to be highly specific and moderately sensitive measures for capturing improvements in disease activity in children with SLE and are likely to provide a conservative estimate of the efficacy of a therapy.[28] In the current analysis, the SRI-4 response at Week 52 consistently favoured belimumab versus placebo. The odds of achieving SRI-4 response after 52 weeks of treatment were 1.49 times higher for children receiving belimumab than those receiving standard therapy alone; this was consistent with the adult studies (range of ORs across the trials: 1.40–1.99). Belimumab-treated patients were also more likely to achieve SRI-6 compared with placebo, in both paediatric and adult studies.

A comparison between the paediatric and adult belimumab studies was possible because the eligibility criteria

**Table 3** Summary of AEs, SAEs and AESIs (mITT or safety population)*

| | cSLE study | | Pooled aSLE studies | |
|---|---|---|---|---|
| | **Placebo (n=40)** | **Belimumab 10 mg/kg intravenously (n=53)** | **Placebo (n=1355)** | **Belimumab 1, 4 and 10 mg/kg intravenously and 200 mg subcutaneously (n=2815)** |
| **Number of patients with ≥1 AE, n (%)** | | | | |
| AE | 33 (82.5) | 42 (79.2) | 1184 (87.4) | 2440 (86.7) |
| Treatment-related AE | 15 (37.5) | 19 (35.8) | 463 (34.2) | 1019 (36.2) |
| SAE | 14 (35.0) | 9 (17.0) | 230 (17.0) | 421 (15.0) |
| AE resulting in study agent discontinuation | 5 (12.5) | 3 (5.7) | 109 (8.0) | 184 (6.5) |
| Death | 1 (2.5) | 0 (0.0) | 6 (0.4) | 16 (0.6) |
| **Number of patients with ≥1 AESI, n (%)†** | | | | |
| Infections‡ | 3 (7.5) | 7 (13.2) | 97 (7.2) | 173 (6.1) |
| Serious infections | 1 (2.5) | 1 (1.9) | 17 (1.3) | 40 (1.4) |
| All opportunistic infections§ | 0 (0.0) | 1 (1.9) | 92 (6.8) | 157 (5.6) |
| Serious opportunistic infections | 0 (0.0) | 0 (0.0) | 14 (1.0) | 25 (0.9) |
| Active tuberculosis | 0 (0.0) | 1 (1.9) | 5 (0.4) | 4 (0.1) |
| Serious active tuberculosis | 0 (0.0) | 0 (0.0) | 3 (0.2) | 3 (0.1) |
| All herpes zoster | 3 (7.5) | 5 (9.4) | 59 (4.4) | 106 (3.8) |
| Serious herpes zoster | 1 (2.5) | 1 (1.9) | 5 (0.4) | 15 (0.5) |
| Sepsis | 0 (0.0) | 0 (0.0) | 10 (0.7) | 20 (0.7) |
| Serious sepsis | 0 (0.0) | 0 (0.0) | 6 (0.4) | 18 (0.6) |
| Malignancies (including NMSC) | 0 (0.0) | 0 (0.0) | 3 (0.2) | 12 (0.4) |
| Solid tumour | 0 (0.0) | 0 (0.0) | 2 (0.1) | 8 (0.3) |
| Haematological | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Skin | 0 (0.0) | 0 (0.0) | 1 (<0.1) | 4 (0.1) |
| Malignancies (excluding NMSC) | 0 (0.0) | 0 (0.0) | 2 (0.1) | 8 (0.3) |
| Depression/suicide/self-injury | 4 (10.0) | 1 (1.9) | 92 (6.8) | 210 (7.5) |
| Serious depression | 1 (2.5) | 0 (0.0) | 2 (0.1) | 6 (0.2) |
| Serious suicide/self-injury | 2 (5.0) | 0 (0.0) | 4 (0.3) | 4 (0.1) |
| Post-infusion systemic reactions | 3 (7.5) | 4 (7.5) | 110 (8.1) | 286 (10.2) |
| Serious post-infusion systemic reactions/hypersensitivity | 0 (0.0) | 0 (0.0) | 2 (0.1) | 13 (0.5) |

*mITT population for PLUTO, BLISS-52, BLISS-76, LBSL02 and BLISS-SC, and safety population for BLISS-NEA and EMBRACE.
†AESI occurring in ≥1 patient in both treatment groups in either PLUTO or the pooled adult studies.
‡Infections of special interest only (opportunistic infections, herpes zoster, tuberculosis and sepsis).
§Per sponsor adjudication.
AE, adverse event; AESI, adverse events of special interest; aSLE, adult-onset systemic lupus erythematosus; cSLE, childhood-onset systemic lupus erythematosus; mITT, modified intention-to-treat; NMSC, non-melanoma skin cancer; SAE, serious adverse event.

of PLUTO were generally similar to those of the phase III intravenous belimumab adult studies with respect to baseline disease activity.[15–17 19 20] An exception was the LBSL02 study,[25] which did not require patients to be antibody-positive and the minimum SELENA-SLEDAI threshold requirement was lower than in other studies; thus, it was only considered in the safety comparisons. It should be noted that we excluded studies of subcutaneous belimumab in the efficacy analysis because the respective paediatric study has not been completed (NCT04179032) and

subcutaneous belimumab is not approved for paediatric use; however, adult patients from the BLISS-SC study[18] were included in safety comparisons.

The PLUTO study was not powered statistically to test for treatment differences between belimumab and placebo due to challenges in enrolling sufficient patients with cSLE; instead, it was designed to descriptively evaluate the efficacy and safety of belimumab in cSLE in a randomised placebo-controlled clinical trial. Besides the SRI,[28] there are also paediatric-specific provisional

response criteria for cSLE that have been developed by the Pediatric Rheumatology International Trials Organization (PRINTO) and the American College of Rheumatology (ACR).[29–31] When used in the PLUTO study, the PRINTO/ACR criteria of improvement showed clear discrimination in improvement between the belimumab and the placebo group (PRINTO/ACR 30: 28/53 (52.8%) vs 11/40 (27.5%), OR 2.92 (95% CI 1.19 to 7.17); PRINTO/ACR 50: 32/53 (60.4%) vs 14/40 (35.0%), OR 2.74 (95% CI 1.15 to 6.54)).[20]

A previous pooled analysis of the BLISS-52 and BLISS-76 studies found that adults with higher baseline disease activity (denoted by a higher SELENA-SLEDAI score, seropositive for anti-dsDNA antibodies or low complement C3/C4 levels) showed greater SRI response (OR 95% CI) to belimumab versus placebo than patients without these characteristics.[27] The current analysis demonstrated that a greater proportion of adult patients with baseline SELENA-SLEDAI score $\geq$10 achieved an SRI-4 response than patients with baseline SELENA-SLEDAI score $\leq$9 across all studies, although in PLUTO treatment differences versus placebo in SRI-4 responses were the same in both subgroups (OR: 1.50). In contrast to previous studies, when analysed by baseline biomarker levels, more patients with cSLE with baseline normal/high C3/C4 and low anti-dsDNA achieved SRI-4 response at Week 52 than patients with baseline low C3/C4 levels and anti-dsDNA $\geq$30 IU/mL. In the adult studies, treatment differences versus placebo in SRI-4 responses were greater in patients with baseline low C3/C4 levels and anti-dsDNA $\geq$30 IU/mL than in patients with baseline normal/high C3/C4 and low anti-dsDNA. The observed differences between paediatric and adult patients with SLE could be due to the small sample size in the paediatric study or differences in disease biology between age groups. It should also be noted that this study was not powered to look at individual subgroups and therefore the results should be interpreted with caution.

In children, belimumab reduced the risk of severe flares by 64% versus standard therapy, which was more pronounced than what was observed in the adult studies (23%–50%). The greater reduction in flare risk in children seemed to be driven by the high rate of severe flare in the placebo group in PLUTO (35.0%). This observation confirms prior research showing that cSLE is more severe compared with aSLE and may underscore the importance of belimumab use in paediatric patients to avoid damage accumulation mediated by the occurrence of severe flares.

The reduction in prednisone use in the trials of belimumab was modest. This is likely a reflection of the study design where prednisone tapering was left at the discretion of the treating physician. Nonetheless, there were favourable trends towards reduced prednisone use with belimumab compared with placebo in the aSLE studies. The apparent lack of difference in the proportion of patients with a reduction in prednisone dose between belimumab and placebo in cSLE can be probably explained by the small sample size of the PLUTO study or the more liberal use of prednisone in cSLE compared with aSLE.

Overall safety findings in PLUTO were consistent with the adult studies, and no new safety signals were identified in children. Belimumab use in cSLE was associated with more infections of special interest, compared with standard therapy, while in adult studies the rate was similar in both groups. The predominant infection of special interest in PLUTO was herpes zoster; treatment with glucocorticoids or standard immunosuppressants may be contributing factors.[32 33] This stresses the importance of recommending varicella vaccination in patients with cSLE and the need to use corticosteroids parsimoniously in children with SLE.

The rate of serious infections of special interest was low in all patients treated with belimumab, across the age range of SLE. Few malignant neoplasms occurred in the adult studies and none in the PLUTO study. Notably, the incidence of post-infusion systemic reactions was similar in the belimumab and placebo groups in both the paediatric and adult patients enrolled in the clinical studies of belimumab.

A limitation of this across-trial comparative analysis may be the descriptive nature of the comparisons, as no formal statistical analyses were performed. Given that studies were conducted in different geographical areas and because study designs were not identical, summary statistics were not straightforward to calculate. Despite this, the results were generally consistent across studies and demonstrate the efficacy and safety of belimumab in paediatric and adult patients with SLE. The strengths and weaknesses of each study included in this analysis are described in detail in their corresponding publications.[15–20 25]

In conclusion, although multiple factors such as medical cost will affect the choice of medication, the results of this across-trial comparison demonstrate consistent efficacy and safety of belimumab plus standard therapy in paediatric and adult patients with SLE, supporting a favourable benefit/risk profile of belimumab in patients with SLE aged 5 years and older.

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