EXTENDED REPORT

Improvements in health-related quality of life with belimumab, a B-lymphocyte stimulator-specific inhibitor, in patients with autoantibody-positive systemic lupus erythematosus from the randomised controlled BLISS trials

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Handling editor Tore K Kvien

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Accepted 24 February 2013

To cite: Strand V, Levy RA, Cervera R, *et al*. *Ann Rheum Dis* Published Online First: [*please include* Day Month Year] doi:10.1136/annrheumdis-2012-202865

ABSTRACT

Objective Assess the effects of belimumab treatment plus standard systemic lupus erythematosus (SLE) therapy on health-related quality of life (HRQOL) in patients with active, autoantibody-positive SLE.

Methods Patients received standard therapy plus placebo or belimumab 1 or 10 mg/kg in two multicentre, randomised controlled trials of 52 (BLISS-52; N=865) and 76 (BLISS-76; N=819) weeks' duration. Responders were evaluated by SLE Responder Index at week 52. Patient-reported outcome assessments included SF-36, Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue, and EQ-5D.

Results Mean SF-36 Physical Component Summary (PCS) scores at week 24 was a major secondary endpoint. Baseline SF-36 scores were 1.5 SDs below age-/sex-matched US norms with similar improvement at week 24 across treatment groups. Mean changes from baseline in PCS scores were significantly ($p<0.05$) greater with belimumab 1 mg/kg (4.20) and 10 mg/kg (4.18) versus placebo (2.96) in BLISS-52, week 52. In BLISS-76, significantly ($p<0.05$) greater improvements were seen with belimumab 1 mg/kg in PCS (belimumab 1 mg/kg=4.37, 10 mg/kg=3.41 vs placebo=2.85) and Mental Component Summary (MCS) scores (belimumab 1 mg/kg=3.14, 10 mg/kg=2.70 vs placebo=1.40) at week 52, and in MCS score at week 76 (belimumab 1 mg/kg=3.05, 10 mg/kg=2.28 vs placebo=1.36). In pooled analysis, significantly greater improvements in PCS, SF-36 vitality domain, and FACIT-Fatigue scores at week 52 were evident with both belimumab doses.

Conclusions The clinically meaningful improvements in HRQOL in autoantibody-positive patients with active SLE treated with belimumab and standard therapy are consistent with the reductions in disease activity observed in these trials.

ClinicalTrials.gov number NCT00424476, NCT00410384.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease that may affect multiple body organs and systems, and is characterised by relapses and remissions.[1 2] Patients with SLE have an increased risk for mortality compared with age-matched and sex-matched healthy subjects, as well as for comorbidities resulting from the disease and its treatment, which adversely affect health-related quality of life (HRQOL).[1 3] The effects of SLE on HRQOL are comparable with, or worse than, those of other chronic diseases, such as AIDS, rheumatoid arthritis, diabetes and congestive heart failure.[2 4–6] Fatigue is a common complaint of patients with SLE, and is associated with poor physical and mental functioning.[7]

B-lymphocyte stimulator (BLyS), an immunomodulatory cytokine that promotes B-cell survival and differentiation, and immunoglobulin class switching, is overexpressed in many patients with autoimmune diseases, including SLE.[8 9] Significant associations have been observed between plasma BLyS levels and markers of SLE disease activity.[9] Belimumab is a human, immunoglobulin-G1λ monoclonal antibody that inhibits the biologic activity of soluble BLyS.[10] In two phase 3, randomised, double-blind, multicentre, placebo-controlled trials (BLISS-52 (N=865; ClinicalTrials.gov identifier NCT00424476) and BLISS-76 (N=819; NCT00410384)), belimumab treatment was efficacious with an acceptable safety profile in patients with autoantibody-positive SLE.[11 12] This report presents the results of patient-reported outcomes, including HRQOL, from these phase 3 trials.

METHODS

Trial design

Details of the trial designs and methods–similar in both BLISS-52 and BLISS-76–have been described previously.[11 12] The trials were conducted in accordance with the Declaration of Helsinki. The protocols were reviewed and approved for all study sites by a central institutional review board, and all patients provided written informed consent. In brief, adult patients with SLE who were autoantibody positive (antinuclear antibody titre ≥1 : 80, or antidouble-stranded DNA antibodies ≥30 IU/ml) and had active disease (Safety of Estrogens in Lupus Erythematosus National Assessment-SLE Disease Activity Index (SELENA-SLEDAI) score

≥6) at screening were enrolled, having received a stable regimen of standard SLE therapy for ≥30 days, including prednisone, and nonsteroidal anti-inflammatory, antimalarial and immunosuppressive drugs. Exclusion criteria included severe active SLE nephritis or severe central nervous system manifestations of lupus. In addition to standard therapy, patients were randomly assigned to receive placebo, or belimumab 1 or 10 mg/kg. These studies were designed to compare belimumab with placebo, as all patients were receiving active therapy prior to enrolment and during the trials. Treatments were administered intravenously on days 0, 14 and 28, and every 28 days thereafter through week 48 in BLISS-52 and week 72 in BLISS-76. The primary efficacy endpoint was SLE Responder Index (SRI) rate at week 52.[13] To be considered an SRI responder, a patient had to have a ≥4-point reduction in SELENA-SLEDAI score, no new British Isles Lupus Assessment Group A and <2 new B scores, and 'no deterioration' (eg, <0.3-point increase) in Physician's Global Assessment score at week 52 compared with baseline.

A major secondary endpoint was mean change in SF-36v2 Health Survey Physical Component Summary (PCS) scores at week 24.[11 12] Additional prespecified secondary endpoints included mean changes from baseline in SF-36 PCS, Mental Component Summary (MCS), and domains, Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) V.4, and EQ-5D scores at weeks 12, 24, 52 and 76 (BLISS-76 only). Additional posthoc analyses were performed using data from these measures.

The SF-36 is a generic, validated questionnaire that assesses HRQOL during the previous 4 weeks in 8 domains, including physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health.[14 15] It has been validated and tested in many SLE trials and across cultures.[6 16 17] Raw domain scores are converted to a 0–100 scale, with higher scores indicating better health. These scores are Z-transformed and weighted to yield values used to calculate PCS and MCS scores, which are norm based with a mean of 50 and SD of 10. Minimum clinically important differences (MCID) for improvement and deterioration, respectively, in summary scores are +2.5 and −0.8, and +5.0 and −2.5 for domain scores.[18] SF-36 also includes a transition question–'Compared to 1 year ago, how is your general health today?'–which includes five response categories from 'much worse' to 'much better'.

Spydergrams present data for each SF-36 domain along individual spokes, ranging from 0 (worst health) to 100 (best health) and have been used to visualise HRQOL changes in response to treatment in patients with autoimmune diseases; gridlines represent 10 points, for instance, 2× MCID.[19 20] Mean SF-36 domain scores in patients at baseline and week 52 in both BLISS studies were compared with age-matched and sex-matched healthy US subjects. With the innermost polygon representing baseline SF-36 domain values for SLE patients in the BLISS studies, and the outermost polygon representing domain scores of comparable healthy subjects, mean improvements from baseline with treatment are illustrated by the intermediate rings.

The FACIT-Fatigue scale is based on a 13-question questionnaire that assesses fatigue during the previous 7 days, scored from 0 to 52 (worst); MCID is 4.0. The FACIT-Fatigue scale has been validated in patients with rheumatoid arthritis.[18 21 22]

The EQ-5D questionnaire provides a profile of five dimensions (ie, mobility, self-care, usual activities, pain/discomfort and anxiety/depression), with three responses for each: 'no', 'some or moderate', and 'severe' problems.[23] A summary index is calculated by weighting the answers based on health states in a population sample. In the present study, EQ-5D scores were calculated using US and UK value sets.[23 24] The index ranges from 1 (perfect health) to <0, which represents the worst imaginable state of health. The EQ-5D includes the EuroQoL visual analogue scale (EQ VAS), a vertical 20 cm VAS used to score the patient's health perception, with 100 representing the best and 0 the worst health.

The SF-36, FACIT-Fatigue, and EQ-5D were administered at baseline, and weeks 4, 8, 12, 24 and 52 in both trials, and additionally at weeks 20, 32, 40, 48, 68 and 76 in BLISS-76 and week 36 in BLISS-52.

Statistical analyses

Primary analyses were evaluated by individual study. Changes from baseline in SF-36, FACIT-Fatigue, and EQ-5D scores were analysed using a covariance model, with covariates for baseline value and the three stratification factors, including baseline SELENA-SLEDAI score (≤9 vs ≥10), baseline proteinuria level (<2 g/24 h vs ≥2 g/24 h equivalent), and race (African descent or indigenous American descent vs other). The trial was also a covariate for the prespecified pooled analyses. The last observation was carried forward to account for missing data in SF-36 and FACIT-Fatigue analyses, whereas only observed values were included in the EQ-5D analysis. Where baseline data are presented as combined for all treatment groups, significance testing was based on change from baseline within each treatment group. Nominal p values are from pairwise comparisons of active treatments versus placebo, and a value <0.05 was considered significant. Due to the similar study designs of BLISS-52 and BLISS-76, data from both trials were pooled by treatment group for analyses in HRQOL measures.[11 12]

RESULTS

Baseline characteristics

Patient demographics and disease characteristics were well balanced between treatment groups within each trial at baseline (table 1).[11 12] There were, however, some differences between the BLISS-52 and BLISS-76 study populations in race, age, disease duration and activity, and types of background standard therapies used that can, in part, be attributed to the varied geographic locations of the studies. Patients in BLISS-76 had a longer duration of SLE and more damage, as measured by the Systemic Lupus International Collaborating Clinics Damage Index, whereas those in BLISS-52 were more serologically active. The proportions of patients taking prednisone, and mean prednisone (or equivalent) doses were higher, and immunosuppressant use was lower in BLISS-52 than in BLISS-76. Baseline SF-36 scores in both study populations were lower than those of an age-matched and sex-matched US population.

Primary efficacy endpoint

As previously reported, SRI rates at week 52 in BLISS-52 were significantly higher with belimumab 1 mg/kg (51%; p=0.01) and 10 mg/kg (58%; p<0.001) than with placebo (44%); corresponding rates were 41% (p=0.09) and 43% (p=0.02) vs 33.5% in BLISS-76, and 46% (p=0.006) and 51% (p<0.001) vs 39% in pooled analysis.[11 12]

SF-36 outcomes

Baseline PCS scores were lower than MCS scores in both trials: ~1 (BLISS-52) and 1.5 (BLISS-76) SDs below normative values of 50 (table 1 and figure 1). Mean PCS scores improved from baseline to week 24 in all treatment groups, but were not significantly different between groups (major secondary endpoint).[11 12]

Table 1 Baseline demographics and patient characteristics

	BLISS-52 (N=865)	BLISS-76 (N=819)
Region/country, %		
US/Canada	–	53.2
Western Europe/Israel	–	24.7
Americas excluding US/Canada	49.5	10.7
Asia–Pacific	39.2	–
Eastern Europe	11.3	11.4
Mean age±SD, years	35.5	40.2
Sex, %		
Women	94.9	93.3
Race, %		
Asian	37.8	3.4
Indigenous American*	32.3	12.6
White/Caucasian	26.5	69.5
Black/African–American	3.5	14.4
Multiracial/other	0.6	1.0
SLE characteristics		
Mean SLE duration±SD, years	5.3±5.3	7.5±7.1
Mean SELENA-SLEDAI±SD	9.8±3.8	9.7±3.8
BILAG 1 A or 2 B, %	58.3	63.5
BILAG 1 A, %	19.0	12.1
Mean SLICC damage index score	0.57	1.00
ANA ≥1 : 80, %	93.9	92.1
Anti-dsDNA ≥30 IU/ml, %	74.5	64.0
Low C3 (<90 mg/dl), %	49.4	40.4
Low C4 (<16 mg/dl), %	59.3	52.6
Anti-dsDNA and low C3/C4, %	55.5	44.5
Prednisone use, %	96.0	76.1
Mean prednisone±SD, mg/d†	12.7±8.4	8.8±8.2
Dose >7.5 mg/d, %	69.4	45.9
Immunosuppressive use, %‡	42.2	55.6
Antimalarial use, %	67.2	63.4
HRQOL scores		
SF-36 PCS, n	853	813
Mean score±SD	41.5±9.0	36.5±9.7
SF-36 MCS, n	853	813
Mean score±SD	40.7±10.5	41.0±12.0
SF-36 vitality, n	863	816
Mean score±SD	48.9±20.3	37.2±21.8
FACIT-Fatigue, n	842	812
Mean score±SD	33.5±10.2	26.6±12.4

*Alaska native or American Indian from North/South/Central America.
†Prednisone or prednisone equivalent.
‡Includes azathioprine, azathioprine sodium, ciclosporin, cyclophosphamide, leflunomide, methotrexate, methotrexate sodium, mizoribine, mycophenolate mofetil, mycophenolate sodium, mycophenolic acid and thalidomide.
ANA, antinuclear antibody; anti-dsDNA, antidouble-stranded DNA; BILAG, British Isles Lupus Assessment Group; C, complement; FACIT, Functional Assessment of Chronic Illness Therapy; HRQOL, health-related quality of life; MCS, Mental Component Summary; PCS, Physical Component Summary; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment–Systemic Lupus Erythematosus (SLE) Disease Activity Index; SF-36, Short Form-36; SLE, systemic lupus erythematosus; SLICC, Systemic Lupus International Collaborating Clinics.

Both PCS and MCS scores improved over time, and were greater with belimumab than placebo in both trials at week 52 (figure 1). In BLISS-52, patients in both belimumab treatment groups reported significantly greater improvements ($p<0.05$) in PCS scores versus placebo at week 52 (belimumab 1 mg/kg=4.20 and belimumab 10 mg/kg=4.18 vs placebo=2.96). In BLISS-76, improvements in PCS and MCS scores were significantly greater with belimumab 1 mg/kg versus placebo at week 52 (PCS: belimumab 1 mg/kg=4.37 vs placebo=2.85 and MCS: belimumab 1 mg/kg=3.14 vs placebo=1.40; both $p<0.05$), and in MCS scores at week 76 (belimumab 1 mg/kg=3.05 vs placebo=1.36; $p<0.05$), whereas mean changes in PCS and MCS scores with belimumab 10 mg/kg were not significantly different (PCS week 52=3.41, MCS week 52=2.70, and MCS week 76=2.28). Pooled data showed significantly greater improvements at week 52 in PCS scores with both belimumab doses versus placebo ($p<0.05$), and in MCS scores with 1 mg/kg ($p<0.01$).

The spydergram in figure 2A illustrates the mean SF-36 domain scores at baseline and week 52 in BLISS-52 patients compared with age-matched and sex-matched US subjects. The mean scores of healthy subjects serve as a benchmark comparator, and the large decrements from normative values at baseline across all domains reveal the broad impact of active SLE in patients. In BLISS-52, mean changes from baseline at week 52 were significantly higher in the physical functioning, bodily pain and role-emotional domains with both belimumab doses, in the social functioning and general health domains with belimumab 1 mg/kg, and in the vitality domain with 10 mg/kg versus placebo ($p<0.05$ for all). Reported improvements from baseline in all eight domains with belimumab 1 and 10 mg/kg exceeded placebo and were ≥MCID.

In BLISS-76, reported improvements with belimumab 1 mg/kg in the SF-36 role-physical, bodily pain, general health and vitality domains at week 52 were significantly different from placebo, and mean changes from baseline in all eight domains were ≥MCID. Patients receiving belimumab 10 mg/kg did not report statistically significant improvements, although all except the role-emotional domain score were clinically meaningful (≥MCID) (figure 2B). The impact of SLE on HRQOL was more evident in BLISS-76 than in BLISS-52, reflecting increased disease duration and more severe disease activity, as indicated by lower baseline SF-36 domain scores.

In the pooled phase 3 studies, mean changes from baseline at week 52 were significantly higher in the physical functioning, bodily pain, general health and vitality domains with both belimumab doses, and in the social functioning and role-emotional domains with belimumab 1 mg/kg versus placebo ($p<0.05$ for all). In all eight domains, reported improvements from baseline with belimumab 1 and 10 mg/kg were ≥MCID, and all except the role-physical domain for belimumab 10 mg/kg exceeded improvements with placebo treatment (figure 2C).

In BLISS 52, responses to the SF-36 transition question at week 52 indicated that patients receiving belimumab versus placebo reported their health as being 'better' or 'much better' than 1 year prior (64.2% and 64.5% with 1 and 10 mg/kg, respectively, vs 52.6% with placebo; $p<0.01$). In BLISS-76, differences were not statistically significant (although numerically greater) in the belimumab groups at weeks 52 (47.2% and 45.2% with 1 and 10 mg/kg, respectively, vs 41.5% with placebo) and 76 (41.7% and 41.4% vs 38.2%). In pooled analysis, 56% ($p=0.003$) and 55% ($p=0.007$) of patients receiving belimumab 1 and 10 mg/kg, respectively, reported that their health was 'better' or 'much better' versus 47% receiving placebo.

FACIT-Fatigue outcomes

Although FACIT-Fatigue scores were not significantly different across treatment groups at the week-24 prespecified secondary endpoint, scores from baseline to week 52 improved significantly ($p<0.05$) with belimumab 1 and 10 mg/kg vs placebo in BLISS-52, and with 1 mg/kg at weeks 52 and 76 secondary endpoints in BLISS-76 (figure 3A,B). While differences observed between belimumab 10 mg/kg and placebo were not statistically

significant in BLISS-76, numerical improvements over placebo were observed by week 8 and sustained through week 76. In pooled analysis, FACIT-Fatigue scores were significantly improved ($p<0.05$) with both belimumab dosages at week 52 (figure 3C), as well as weeks 8 and 12 (data not shown). Reported improvements in FACIT-Fatigue were associated with those in the SF-36 vitality domain, where statistically significant improvements (mean change from baseline±SE) with belimumab versus placebo were reported at weeks 8 (7.58±0.78) and 12 (8.49±0.84) with 10 mg/kg (both $p<0.05$),

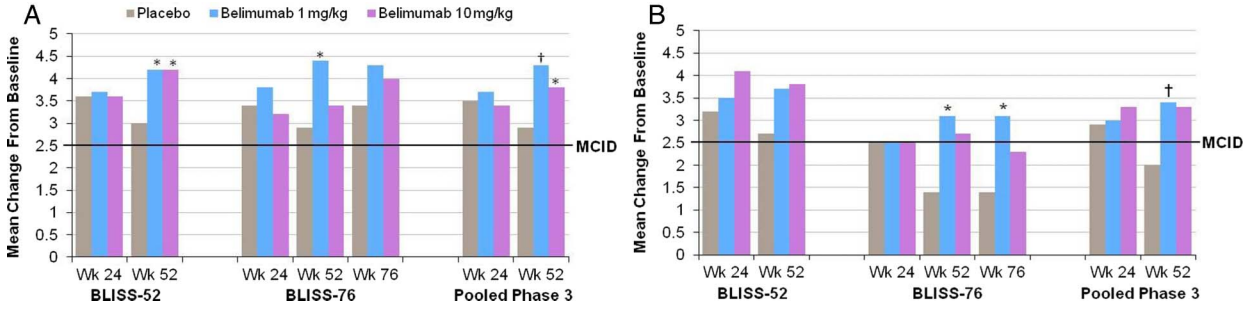

Figure 1 Last observation carried forward analysis of mean changes in (A) SF-36 Physical Component Summary and (B) Mental Component Summary scores for weeks 24 and 52 in BLISS-52 and pooled phase 3 studies, and weeks 24, 52 and 76 in BLISS-76. *p<0.05; †p<0.01. MCID, minimum clinically important difference.

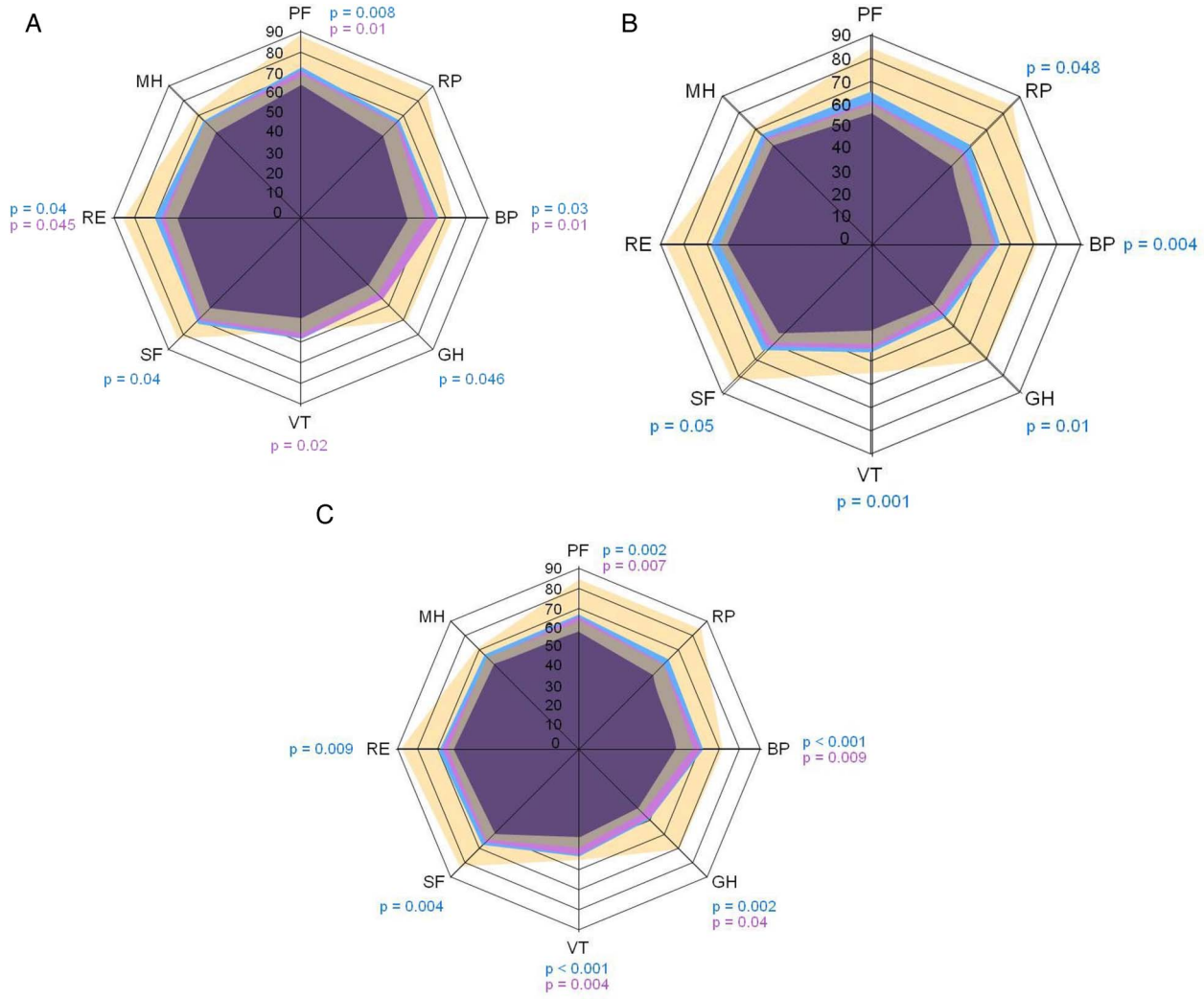

Figure 2 Spydergrams of composited baseline (BL) and week-52 SF-36 domain scores by treatment group versus US age-/gender (A/G)-matched norms in (A) BLISS-52, (B) BLISS-76, and (C) pooled analysis. Inner polygon (deep purple) represents weighted mean BL SF-36 domain scores across all three treatment groups; outer polygon (yellow) represents A/G norms as a benchmark comparison; mean changes with placebo, and belimumab 1 and 10 mg/kg shown as intermediate polygons (grey, blue, and light purple, respectively). BP, bodily pain; GH, general health; MH, mental health; PF, physical functioning; RE, role-emotional; RP, role-physical; SF, social functioning; VT, vitality.

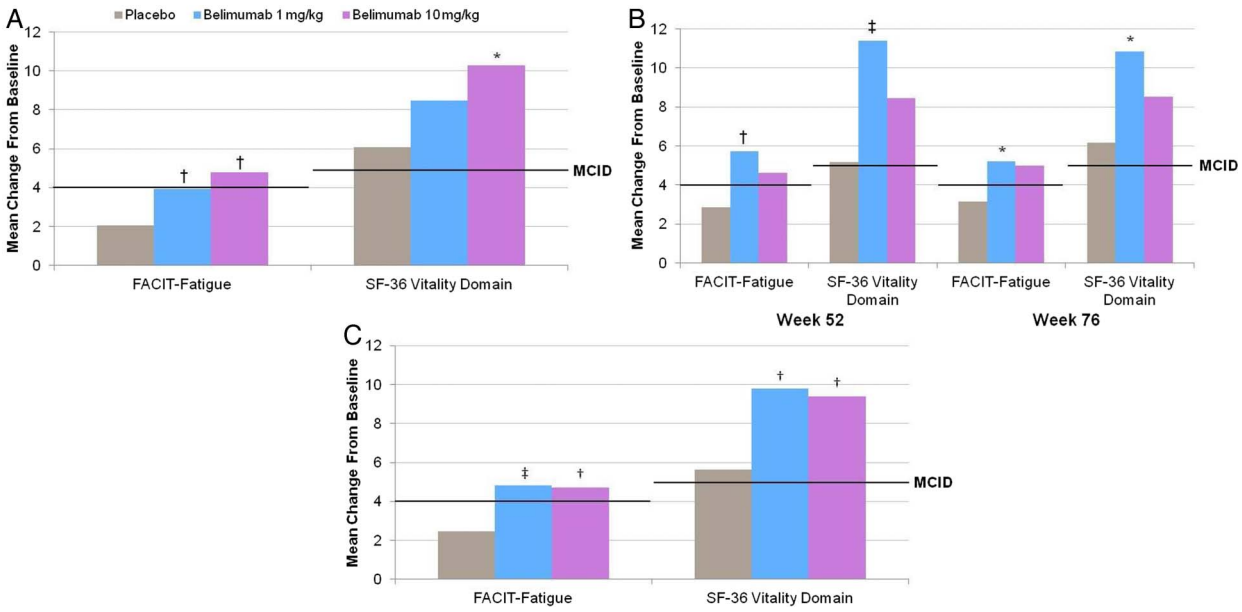

Figure 3 Last observation carried forward analysis of mean changes from baseline in Functional Assessment of Chronic Illness Therapy-Fatigue and SF-36 vitality domain scores for (A) BLISS-52 at week 52, (B) BLISS-76 at weeks 52 and 76, and (C) pooled phase 3 data at week 52. Higher scores indicate less fatigue and increased vitality. *p<0.01; †p<0.05; ‡p<0.001. The p values were obtained from an ANCOVA model for the comparison between each belimumab treatment group and the placebo group. ANCOVA, analysis of covariance; MCID, minimum clinically important difference.

and at week 52 with both 1 mg/kg (9.78±0.80; p<0.001) and 10 mg/kg (9.40±0.87; p<0.01). The coefficient of correlation between FACIT-Fatigue and the SF-36 vitality domain was 0.6998 at week 52.

EQ-5D

In BLISS-52, mean changes from baseline to week 52 in the EQ-5D utility index (based on the US or UK value set) and VAS scores were not significantly different between treatment groups (table 2; UK data not shown). Significant differences were, however, seen in the percentages of patients with no problems for the mobility question with belimumab 1 mg/kg and for the pain/discomfort question with belimumab 10 mg/kg versus placebo at week 52. In BLISS-76, the EQ-5D VAS score significantly improved with belimumab 1 mg/kg at week 52, without significant between-treatment differences in the utility index or component questions. In pooled analysis, the only significant between-treatment difference at week 52 in EQ-5D measures was for the pain/discomfort question with belimumab 10 mg/kg versus placebo.

DISCUSSION

Patients receiving belimumab reported clinically meaningful improvements in HRQOL and fatigue at week 52 versus placebo in both individual BLISS studies and by pooled analyses. The major secondary HRQOL endpoint in each trial of greater improvement in SF-36 PCS in the belimumab treatment arms at week 24 was not achieved as the improvements were similar in all treatment groups. However, at week 52, mean PCS scores improved significantly with belimumab 1 and 10 mg/kg versus

Table 2 EQ-5D at week 52

	BLISS-52			BLISS-76			Pooled		
	Placebo (n=287)	Belimumab 1 mg/kg (n=288)	Belimumab 10 mg/kg (n=290)	Placebo (n=275)	Belimumab 1 mg/kg (n=271)	Belimumab 10 mg/kg (n=273)	Placebo (n=562)	Belimumab 1 mg/kg (n=559)	Belimumab 10 mg/kg (n=563)
Mean utility (US) change from BL±SE	0.05±0.01	0.04±0.01	0.06±0.01	0.05±0.01	0.06±0.01	0.06±0.01	0.05±0.01	0.05±0.01	0.06±0.01
Mobility†	–	8.79*	8.07	–	0.31	−0.33	–	4.79	4.16
Self-care†	–	4.54	3.98	–	1.35	3.36	–	3.04	3.70
Usual activities†	–	1.30	4.01	–	4.77	−5.31	–	2.92	−0.29
Pain/discomfort†	–	0.71	9.30*	–	6.39	2.85	–	3.38	6.33*
Anxiety/depression†	–	4.47	3.93	–	6.17	-0.82	–	5.28	1.71
Mean EQ-5D VAS score change from BL±SE	9.92±1.18	9.77±1.13	9.99±1.23	7.93±1.34	12.11±1.27*	8.04±1.48	8.99±0.89	10.88±0.85	9.10±0.95

*p≤0.05. The p values were obtained from an ANCOVA model for the comparison between each belimumab treatment group and the placebo group.
†Observed difference from placebo at week 52, %.
ANCOVA, analysis of covariance; BL, baseline; VAS, visual analogue scale.

placebo in BLISS-52 and the pooled analysis, and with 1 mg/kg in BLISS-76. Improvements in PCS scores over 52 weeks were also observed in the phase 2 belimumab dose-ranging trial.[25] Mean MCS score improvements were significantly higher with belimumab 1 mg/kg versus placebo in BLISS-76 and the pooled analysis. These improvements in patient outcomes are consistent with the clinical benefits observed in both BLISS trials.[11 12 26–28] Significantly more patients with persistently autoantibody-positive SLE who received belimumab plus standard SLE therapy exhibited reduced disease activity than did those treated with placebo plus standard therapy. The SRI rates were significantly higher with belimumab 1 and 10 mg/kg in BLISS-52, and with 10 mg/kg in BLISS-76, versus placebo and had a greater magnitude of effect in patients with high disease or serologic activity.[28] Further, in pooled analyses, there were reductions in severe flares and corticosteroid use, and improvements in biomarkers and a variety of organ systems commonly affected by SLE.[11 12 26 27]

In BLISS-76, the 1 mg/kg dose HRQOL effect was sometimes similar to or greater than the 10 mg/kg dose as the SRI treatment effect between belimumab doses was diminished compared with BLISS-52. In addition, belimumab was added to standard therapy, for instance, corticosteroids and immunosuppressives. Changes in this background 'active' therapy were allowed; adjustments to immunosuppressives were allowed through week 16 and to corticosteroids through week 24, with tapering at the investigator's discretion over weeks 44–52. This served to 'rescue' patients receiving placebo plus standard therapy, and thereby diminish the differences in responses between each of the active and control treatment groups.

Divergence in improvements from baseline in some HRQOL measures between belimumab and placebo became apparent only after week 24. Given that changes in background medications were allowed initially, and restricted beginning at week 16 for immunosuppressive and antimalarial agents, and at week 24 for prednisone doses, this is not unexpected. In combined analyses, consistent with more increases in prednisone doses in patients receiving placebo[11 12] and with successful tapering to doses ≤7.5 mg qd in patients treated with belimumab,[11 12] patient-reported HRQOL and fatigue also improved. Mean improvements in FACIT-Fatigue scores, which closely correlated with SF-36 vitality domain scores, were also in accordance with PCS scores, reflecting significant improvements (that exceeded MCID for each patient outcome) versus placebo at week 52 with belimumab 1 and 10 mg/kg in BLISS-52 and the pooled analysis, and with 1 mg/kg in BLISS-76. Consistent responses in FACIT-Fatigue scores and the SF-36 vitality domain, which also asks about 'pep' and 'energy,' are supported by a high correlation (r=0.73–0.84) between these measures in patients with rheumatoid arthritis.[21] Improvement in fatigue in SLE is important as it remains among the most frequent complaints (occurring in 81% of patients), and can impact overall HRQOL and the ability to maintain a full-time job.[29 30] In addition, the EQ-5D health utility measure results supported the belimumab improvements observed in other patient-reported outcomes performed in the BLISS trials.

One of the limitations of this analysis of patient outcomes in the BLISS trials was that the individual studies were not powered to detect significant differences in SF-36, FACIT-Fatigue, and EQ-5D scores with belimumab treatment plus standard therapy versus standard therapy alone. Posthoc analysis of pooled data, therefore, shows a more consistent HRQOL and patient-outcome benefit in patients treated with belimumab than in the individual trials, where favourable effects on patient outcomes did not always reach statistical significance. The wide variety of standard therapies, progressive restriction on concurrent immunosuppressive therapy, and variable organ system manifestations may have confounded interpretation of the data. Further study of patient-outcome measures in future belimumab randomised controlled trials in general SLE and lupus nephritis are needed to validate the findings reported in the present analysis.

In summary, the improvements in patient-reported outcomes evident in these phase 3 trials were consistent with other reported clinical benefits of belimumab treatment, such as reduction in severe flares and corticosteroid use, in patients with autoantibody-positive SLE who were also receiving standard SLE therapy.

Acknowledgements Editorial support (writing assistance, assembling figures and tables, collating author comments, grammatical editing and referencing) was provided by Eleanore Gross and Geoff Marx of BioScience Communications, New York, NY , USA.

Collaborators BLISS-52 and BLISS-76 Study Groups.

Contributors All authors have read and approved the manuscript. VS participated in study design, data analysis and interpretation, and manuscript drafting and revision. RAL, RC, MAP, WWF, ZJZ and AEC participated in study design, data acquisition, analysis and interpretation, and manuscript drafting and revision. HB participated in data analysis and interpretation, and manuscript drafting and revision.

Funding This study was funded by Human Genome Sciences, Rockville, Maryland, USA, and GlaxoSmithKline, Uxbridge, UK.

Competing interests VS and MAP have received consultancy fees from GlaxoSmithKline (GSK) and Human Genome Sciences (HGS). RAL has received consultancy fees or honoraria and travel support from GSK and HGS, and board membership and speaker fees from GSK. RC has received consultancy fees or honoraria, travel support, and board membership and educational presentation development fees from GSK and HGS. HB is an employee of and holds stock in GSK. WWF and ZJZ are employees of and hold stock in HGS. AEC has received consultancy fees from GSK and HGS, and grant support for her institution, and speaker fees and travel support from GSK.

Ethics approval The protocols were reviewed and approved for all study sites by a central institutional review board.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Additional unpublished data from the belimumab trials will be available on the GSK public Web site: http://www.gsk.com/

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