Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial

Sandra V Navarra, Renato M Guzmán, Alberto E Gallacher, Stephen Hall, Roger A Levy, Renato E Jimenez, Edmund K-M Li, Mathew Thomas, Ho-Youn Kim, Manuel G León, Coman Tanasescu, Eugeny Nasonov, Joung-Liang Lan, Lilia Pineda, Z John Zhong, William Freimuth, Michelle A Petri, for the BLISS-52 Study Group

Summary

Background Systemic lupus erythematosus is a heterogeneous autoimmune disease that is associated with B-cell hyperactivity, autoantibodies, and increased concentrations of B-lymphocyte stimulator (BLyS). The efficacy and safety of the fully human monoclonal antibody belimumab (BLyS-specific inhibitor) was assessed in patients with active systemic lupus erythematosus.

Methods Patients (aged ≥18 years) who were seropositive with scores of at least 6 on the Safety of Estrogens in Lupus Erythematosus National Assessment–Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) were enrolled in a multicentre phase 3 study, which was done in Latin America, Asia-Pacific, and eastern Europe. Patients were randomly assigned by use of a central interactive voice response system in a 1:1:1 ratio to belimumab 1 mg/kg or 10 mg/kg, or placebo by intravenous infusion in 1 h on days 0, 14, and 28, and then every 28 days until 48 weeks, with standard of care. Patients, investigators, study coordinators, and sponsors were masked to treatment assignment. Primary efficacy endpoint was improvement in the Systemic Lupus Erythematosus Responder Index (SRI) at week 52 (reduction ≥4 points in SELENA-SLEDAI score; no new British Isles Lupus Assessment Group [BILAG] A organ domain score and no more than 1 new B organ domain score; and no worsening [<0·3 increase] in Physician's Global Assessment [PGA] score) versus baseline. Method of analysis was by modified intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00424476.

Findings 867 patients were randomly assigned to belimumab 1 mg/kg (n=289) or 10 mg/kg (n=290), or placebo (n=288). 865 were treated and analysed in the belimumab (1 mg/kg, n=288; 10 mg/kg, n=290) and placebo groups (n=287). Significantly higher SRI rates were noted with belimumab 1 mg/kg (148 [51%], odds ratio 1·55 [95% CI 1·10–2·19]; p=0·0129) and 10 mg/kg (167 [58%], 1·83 [1·30–2·59]; p=0·0006) than with placebo (125 [44%]) at week 52. More patients had their SELENA-SLEDAI score reduced by at least 4 points during 52 weeks with belimumab 1 mg/kg (153 [53%], 1·51 [1·07–2·14]; p=0·0189) and 10 mg/kg (169 [58%], 1·71 [1·21–2·41]; p=0·0024) than with placebo (132 [46%]). More patients given belimumab 1 mg/kg (226 [78%], 1·38 [0·93–2·04]; p=0·1064) and 10 mg/kg (236 [81%], 1·62 [1·09–2·42]; p=0·0181) had no new BILAG A or no more than 1 new B flare than did those in the placebo group (210 [73%]). No worsening in PGA score was noted in more patients with belimumab 1 mg/kg (227 [79%], 1·68 [1·15–2·47]; p=0·0078) and 10 mg/kg (231 [80%], 1·74 [1·18–2·55]; p=0·0048) than with placebo (199 [69%]). Rates of adverse events were similar in the groups given belimumab 1 mg/kg and 10 mg/kg, and placebo: serious infection was reported in 22 (8%), 13 (4%), and 17 (6%) patients, respectively, and severe or serious hypersensitivity reactions on an infusion day were reported in two (<1%), two (<1%), and no patients, respectively. No malignant diseases were reported.

Interpretation Belimumab has the potential to be the first targeted biological treatment that is approved specifically for systemic lupus erythematosus, providing a new option for the management of this important prototypic autoimmune disease.

Introduction

Systemic lupus erythematosus is a multisystem autoimmune disease that results in morbidity, increased mortality rate, and poor quality of life.[1–6] B-lymphocyte stimulator (BLyS), a key survival cytokine for B lymphocytes,[7–9] is overexpressed in patients with systemic lupus erythematosus and other autoimmune diseases.[10–14] In patients with systemic lupus erythematosus, BLyS concentrations are associated with changes in disease activity and anti-dsDNA antibody titres.[10,12–14] Belimumab (Benlysta, Human Genome Sciences, Rockville, MD, USA) is a fully human immunoglobulin (Ig) G1-λ monoclonal antibody that binds to soluble human BLyS and inhibits its biological activity.[15,16] It selectively reduces the numbers of subsets of CD20+ B lymphocytes and short-lived plasma cells, and anti-dsDNA antibody titres in patients with systemic lupus erythematosus.[17]

University of Santo Tomas Hospital, Manila, Philippines (S V Navarra MD); **SaludCoop Clinic, IDEARG, Bogotá, Colombia** (R M Guzmán MD); **Hospital Británico de Buenos Aires, Ciudad Autónoma de Buenos Aires, Argentina** (A E Gallacher MD); **Emeritus Research/Cabrini Hospital, Malvern, VIC, Australia** (S Hall MD); **Hospital Universitário Pedro Ernesto—Universidade Estado do Rio de Janeiro, Rio de Janeiro, Brazil** (R A Levy MD); **Hospital Clínico de Viña del Mar, Viña del Mar, Chile** (R E Jimenez MD); **Prince of Wales Hospital, Hong Kong, China** (E K-M Li MD); **Kerala Institute of Medical Sciences, Kerala, India** (M Thomas MD); **Seoul St Mary's Hospital, Catholic University of Korea, Seoul, Korea** (H-Y Kim MD); **Instituto de Ginecología y Reproducción, Lima, Perú** (M G León MD); **Spitalul Clinic Colentina, Bucureşti, Romania** (C Tanasescu MD); **State Institution, Scientific Research Institute of Rheumatology RAMS, Moscow, Russia** (E Nasonov MD); **Taichung Veterans General Hospital, Taichung, Taiwan** (J-L Lan MD); **Human Genome Sciences, Rockville, MD, USA** (L Pineda MD, Z J Zhong PhD, W Freimuth MD); **and Johns Hopkins University, Baltimore, MD, USA** (M A Petri MD)

Correspondence to:
Dr Michelle A Petri, Johns Hopkins University School of Medicine, Division of Rheumatology, 1830 E Monument St, Ste 7500, Baltimore, MD 21205, USA
mpetri@jhmi.edu

The results of a phase 2, dose-ranging, placebo-controlled trial of belimumab with standard of care in patients with active systemic lupus erythematosus showed that the monoclonal antibody was biologically active and well tolerated.[17] The coprimary endpoints of reduction in Safety of Estrogens in Lupus Erythematosus National Assessment–Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) at week 24 and prolongation of time to first flare over 52 weeks were not achieved. However, in a large proportion of patients (71·5% of overall study population) with seropositive systemic lupus erythematosus–ie, with titres of antinuclear antibody (ANA) of at least 1:80 or concentrations of anti-dsDNA antibody of at least 30 IU/mL–belimumab reduced and stabilised disease activity.[17] The results of an uncontrolled, open-label extension (4 years) of this phase 2 study in patients with systemic lupus erythematosus showed that rates of adverse events, including serious adverse events and infections, stabilised or decreased, and patients who were seropositive had sustained improvement in disease activity, with decreased frequency of flares.[18]

Evidence-based assessment of this phase 2 trial of belimumab in patients with systemic lupus erythematosus resulted in the creation of a new Systemic Lupus Erythematosus Responder Index (SRI), based on improvement in disease activity without worsening of the overall disorder or development of substantial disease activity in new organ systems.[19]

Development of new treatments for systemic lupus erythematosus has been challenging because of the heterogeneity of the disease, variety of disease activity scales that are used, and lack of a contemporary regulatory precedent because no drug has specifically been approved for systemic lupus erythematosus in more than 50 years.[20–24] The aim in this trial was to assess the efficacy, safety, and tolerability of belimumab with standard of care in patients with seropositive systemic lupus erythematosus.

Methods

Patients

In a phase 3 study done in 90 centres in 13 countries in Latin America (Argentina, Brazil, Chile, Colombia, and Peru), Asia-Pacific (Australia, Hong Kong, India, Korea, Philippines, and Taiwan), and eastern Europe (Romania and Russia), patients (aged ≥18 years) who met the American College of Rheumatology criteria for systemic lupus erythematosus[25] and had active disease (score ≥6 at screening on SELENA-SLEDAI)[26] were eligible for enrolment. Other inclusion criteria were unequivocally positive ANA (titre ≥1:80) or anti-dsDNA antibody (≥30 IU/mL), and a stable treatment regimen with fixed doses of prednisone (0–40 mg/day), or non-steroidal anti-inflammatory, antimalarial, or immunosuppressive drugs for at least 30 days before the first study dose. The main exclusion criteria were severe active lupus nephritis or CNS lupus; pregnancy; and previous treatment with any B-lymphocyte-targeted drug (including rituximab), intravenous cyclophosphamide within 6 months of enrolment, and intravenous Ig or prednisone (>100 mg/day) within 3 months.

The study was approved by a central or local institutional review board or ethics committee, and all patients provided written informed consent.

Randomisation and masking

Patients who underwent all screening procedures and met the entry criteria were enrolled in the study and assigned to treatment by use of a central interactive voice response system, with the central randomisation list provided by Human Genome Sciences. Patients were randomised in a 1:1:1 ratio to placebo, or belimumab 1 mg/kg or 10 mg/kg. Randomisation was stratified according to the SELENA-SLEDAI score (6–9 vs ≥10), proteinuria concentration (<2 g/24 h vs ≥2 g/24 h) at screening, and ethnic origin (African descent or indigenous American [Alaska Native or American Indian from North, South, or Central America] vs other). Patients, investigators, study coordinators, and sponsors were masked to treatment assignment during intravenous administration of the drug and assessment of the patients every 4 weeks during the 52-week trial until the database was locked. An unmasked pharmacist prepared unmarked infusion bags for administration. Belimumab and placebo were both prepared as sterile and
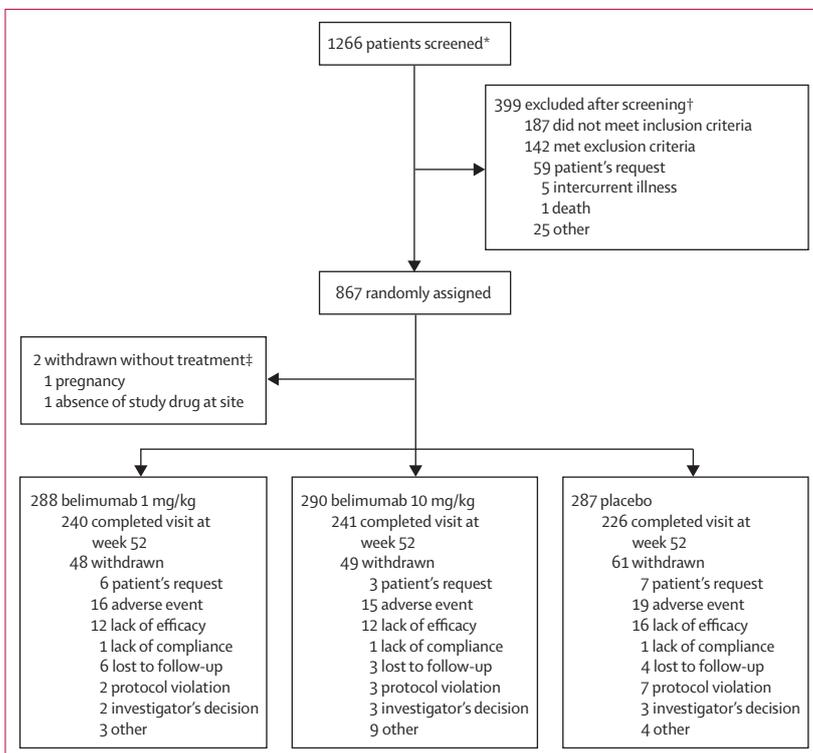

Figure 1: Trial profile
*Patients who were rescreened were counted more than once. †Patients could have more than one reason for being excluded. ‡One patient withdrawn from the belimumab 1 mg/kg group (because of lack of study drug at site) and one from the placebo group (because of pregnancy).

lyophilised vials (5 mL for belimumab 1 mg/kg; 20 mL for belimumab 10 mg/kg and placebo), and contained the same formulations, except without the active drug for placebo.

Study design

Patients were administered the study drug by intravenous infusion in 1 h on days 0, 14, and 28, and then every 28 days until 48 weeks, with standard of care. The regimen for standard of care was based on the patient's disease manifestations and was in accordance with the country's and institution's approach to standard treatment for those disease signs and symptoms, but consistent with the protocol's inclusion and exclusion criteria. Changes to standard of care were restricted after 16 weeks of treatment for immunosuppressive drugs and after 24 weeks for antimalarial drugs. Prednisone dose was not restricted in the first 24 weeks, but required return to within 25% or 5 mg greater than the baseline dose, with no further increases for the remainder of the study. Investigators tapered the prednisone dose on the basis of their clinical judgment. Addition of a new immunosuppressive or biological drug at any time, new antimalarial drug or angiotensin-converting-enzyme inhibitors after 4 months, or statins after 6 months of the study was prohibited. Because angiotensin-converting-enzyme inhibitors can reduce renal proteinuria without affecting the disease activity, the concern was that addition of a new angiotensin-converting-enzyme inhibitor close to the primary end-point could initiate an improvement in renal scores in SELENA-SLEDAI or British Isles Lupus Assessment Group (BILAG)[26–29] without improving long-term disease activity in systemic lupus erythematosus. Rarely, statins can cause symptoms and increases in creatine phosphokinase concentrations that mimic myositis, which could be mistaken for worsening disease activity. Other antihypertensive and lipid-lowering drugs were allowed during the study. Patients who required and took protocol-prohibited drugs during the trial were judged to be treatment failures and discontinued from the study. The activity indices (SELENA-SLEDAI,[26] modified SELENA-SLEDAI Flare Index [SFI],[26,27] BILAG,[28,29] and Physician's Global Assessment [PGA][26]) were assessed every 4 weeks with prescribed laboratory tests, with a final assessment at week 52 by the same trained and qualified principal investigator or subinvestigator. Adverse events, vital signs, concomitant drugs, haematology, chemistry, urinalysis, spot urine protein or creatinine, and pregnancy test results were recorded at every study visit.

Health-related quality of life was assessed with the 36-item Short-Form Health Survey (SF-36; version 2).[30]

Endpoints

The primary efficacy endpoint was the response rate at week 52, assessed with SRI.[19] With the SRI criteria, a responder was defined as having a reduction of at least 4 points in the SELENA-SLEDAI score (defined as clinically meaningful),[31] no new BILAG A organ domain score, no more than 1 new BILAG B organ domain score, and no worsening in PGA score (increase <0·3) at week 52 compared with baseline. The major secondary endpoints were proportion of patients with at least a 4-point reduction from baseline in SELENA-SLEDAI score at week 52, mean change in PGA score at week 24, mean change in SF-36 physical component summary

	Belimumab 1 mg/kg (n=288)	Belimumab 10 mg/kg (n=290)	Placebo (n=287)
Age (years)	35·0 (10·6)	35·4 (10·8)	36·2 (11·8)
Women	271 (94%)	280 (97%)	270 (94%)
Ethnic origin			
Indigenous American*	98 (34%)	92 (32%)	89 (31%)
White	76 (26%)	71 (24%)	82 (29%)
Black American	8 (3%)	11 (4%)	11 (4%)
Asian	106 (37%)	116 (40%)	105 (37%)
Hispanic or Latino	141 (49%)	136 (47%)	143 (50%)
Geographical region†			
Latin America	143 (50%)	140 (48%)	145 (51%)
Asia-Pacific	111 (39%)	119 (41%)	109 (38%)
Eastern Europe	34 (12%)	31 (11%)	33 (11%)
Disease activity			
Disease duration (years)	5·0 (4·6)	5·0 (5·1)	5·9 (6·2)
SELENA-SLEDAI	9·6 (3·8)	10·0 (3·9)	9·7 (3·6)
SELENA-SLEDAI score ≥10	139 (48%)	160 (55%)	158 (55%)
BILAG 1A or 2B score	166 (58%)	172 (59%)	166 (58%)
PGA score	1·4 (0·5)	1·4 (0·5)	1·4 (0·5)
BILAG A or B organ domain scores at baseline			
General	23 (8%)	26 (9%)	28 (10%)
Mucocutaneous	167 (58%)	174 (60%)	172 (60%)
Neurological	1 (<1%)	0	0
Musculoskeletal	150 (52%)	160 (55%)	147 (51%)
Cardiovascular and respiratory	6 (2%)	6 (2%)	12 (4%)
Vasculitis	25 (9%)	33 (11%)	22 (8%)
Renal	48 (17%)	34 (12%)	38 (13%)
Haematology	56 (19%)	53 (18%)	52 (18%)
Proteinuria (g/24 h)	0·6 (1·1)	0·5 (0·9)	0·6 (1·2)
Proteinuria ≥2 g/24 h	26 (9%)	19 (7%)	21 (7%)
Baseline SELENA-SLEDAI organ involvement‡			
CNS	6 (2%)	6 (2%)	5 (2%)
Serosal	10 (3%)	10 (3%)	14 (5%)
Haematological	21 (7%)	16 (6%)	19 (7%)
Constitutional	2 (<1%)	5 (2%)	3 (1%)
Immunological	250 (87%)	248 (86%)	234 (82%)
Musculoskeletal	169 (59%)	174 (60%)	165 (57%)
Dermal	228 (79%)	245 (84%)	236 (82%)
Renal	61 (21%)	52 (18%)	61 (21%)
Vascular	16 (6%)	28 (10%)	20 (7%)
Prednisone	276 (96%)	278 (96%)	276 (96%)
>7·5 mg/day at baseline	204 (71%)	204 (70%)	192 (67%)
Dose (mg/day)	12·9 (8·6)	13·2 (9·5)	11·9 (7·9)
			(Continues on next page)

	Belimumab 1 mg/kg (n=288)	Belimumab 10 mg/kg (n=290)	Placebo (n=287)
(Continued from previous page)			
Immunosuppressive drug§	120 (42%)	123 (42%)	122 (43%)
Mycophenolate	16 (6%)	17 (6%)	19 (7%)
Azathioprine	71 (25%)	84 (29%)	68 (24%)
Methotrexate	24 (8%)	20 (7%)	35 (12%)
Antimalarial (aminoquinolone) drug	195 (68%)	185 (64%)	201 (70%)
Biomarkers			
BLyS ALOD¶	273 (95%)	281 (97%)	273 (95%)
ANA ≥1:80	272 (94%)	276 (95%)	264 (92%)
Anti-dsDNA ≥30 IU/mL	221 (77%)	218 (75%)	205 (71%)
Anti-dsDNA (IU/mL)‖	523·7 (875·7)	603·7 (972·5)	525·8 (851·9)
C3 concentration (g/L)	0·90 (0·30)	0·92 (0·32)	0·94 (0·31)
C3 concentration less than LLN (<0·9 g/L)	148 (51%)	147 (51%)	132 (46%)
C4 concentration (g/L)	0·15 (0·09)	0·15 (0·10)	0·16 (0·10)
C4 concentration less than LLN (<0·16 g/L)	173 (60%)	180 (62%)	160 (56%)
IgG (g/L)**	17·41 (6·24)	17·21 (5·57)	17·16 (5·99)
Hypergammaglobulinaemia (>16·18 g/L)	140 (49%)	151 (52%)	146 (51%)
IgA (g/L)	3·32 (1·41)	3·15 (1·38)	3·12 (1·33)
IgM (g/L)	1·11 (0·65)	1·16 (0·71)	1·17 (0·83)

Data are number (%) or mean (SD). SELENA-SLEDAI=Safety of Estrogens in Lupus Erythematosus National Assessment–Systemic Lupus Erythematosus Disease Activity Index. BILAG=British Isles Lupus Assessment Group. PGA=Physician's Global Assessment. BLyS=B-lymphocyte stimulator. ALOD=above limit of detection (0·5 ng/mL). ANA=antinuclear antibodies. C3=complement C3. C4=complement C4. LLN=lower limit of normal. Ig=immunoglobulin. *Refers to Alaska Native or American Indian from North, South, or Central America. †Latin America included Argentina, Brazil, Chile, Colombia, and Peru; Asia-Pacific included Australia, Hong Kong, India, Korea, Philippines, and Taiwan; and eastern Europe included Romania and Russia. ‡Based on Bombardier and colleagues'[33] SLEDAI organ domain designations. §Excluding aminoquinoline antimalarial drugs (hydroxychloroquine, chloroquine, and mepacrine). ¶Serum BLyS concentrations were only assessed before belimumab dosing because interference from belimumab precluded an accurate measurement of the concentrations. ‖Patients who were positive at baseline with an anti-dsDNA (IgG) assay with a detectable range of 30–3600 IU/mL. **One patient in the belimumab 10 mg/kg group had grade 2 hypogammaglobulinaemia at baseline.

Table 1: Baseline demographic and clinical characteristics of patients

score at week 24, and proportion of patients with an average reduction in prednisone dose of at least 25% from baseline to 7·5 mg/day or less during weeks 40 to 52. Other secondary endpoints included assessment of the three components of SRI with time, rate of and time to flares of systemic lupus erythematosus as measured with SFI,[26,27] BILAG during 52 weeks,[28,29,32] steroid-sparing effects, and biomarker changes from baseline.

Biomarkers
All biomarkers were measured by use of ELISA, except ANA, which was identified with indirect immuno-fluorescence testing on HEP-2 cells (Quest Diagnostics, Van Nuys, CA, USA).

Safety
Adverse events were coded according to the Medical Dictionary for Regulatory Activities' (version 12.0) preferred term or system organ class, and were graded for severity using the Adverse Event Severity Grading Tables, modified from the Division of Microbiology and Infectious Diseases Adult Toxicity Tables (2001).

Statistical analysis
The response rate at week 52 (primary endpoint) was assessed with SRI in each belimumab group and was compared with the placebo group by use of a logistic regression model adjusted for baseline randomisation stratification factors. Analysis was done in a modified intention-to-treat population, defined as all randomly assigned patients who received a dose of the study drug. The sample size of 810 patients (270 per group) was calculated to provide 90% power at a significance level of 5% to detect a 14% absolute improvement in the SRI response rate at week 52 with belimumab 10 mg/kg relative to placebo. A standard deviation of 50% was used to account for the worst-case variability.[17]

In the primary efficacy analyses, a stepdown procedure was used to control the type 1 error (two-sided α=0·05) for comparison of belimumab 10 mg/kg with placebo; if 10 mg/kg was better than placebo, belimumab 1 mg/kg was then compared with placebo. Patients who withdrew or required changes in background drugs for systemic lupus erythematosus that were other than those permitted by protocol were judged to be treatment failures. Binary efficacy variables were assessed with a logistic regression model, continuous variables were analysed with an analysis of covariance model, and time-to-flare variables were analysed by use of a Cox-proportional hazards model. All analyses were adjusted for baseline randomisation factors.

This trial is registered with ClinicalTrials.gov, number NCT00424476.

Role of the funding source
Human Genome Sciences was involved in the conception, design, implementation, and supervision of this study; data analysis and interpretation; statistical analysis; and report drafting and revision. GlaxoSmithKline, Uxbridge, UK, was involved in data interpretation, and report drafting and revision. All authors were responsible for the decision to submit this report for publication and had complete access to the study data on request.

Results
From May 8, 2007, to April 14, 2008, 867 patients with systemic lupus erythematosus were randomly assigned to belimumab 1 mg/kg (n=289) or 10 mg/kg (n=290), or placebo (n=288) in Latin America (n=429), Asia-Pacific (n=339), and eastern Europe (n=99). Figure 1 shows the trial profile. Two of 867 patients never received any study treatment and were excluded; the modified intention-to-treat population was therefore 865 patients who were randomly assigned and treated during the study, and analysed. The three groups did not differ in any of the main baseline characteristics (table 1) or in reasons for discontinuation of treatment (figure 1). Use of immunosuppressive drugs was similar in Asia-Pacific (142 [42%] of 339), Latin America (187 [44%] of 428), and

	Belimumab 1 mg/kg (n=288)	Belimumab 10 mg/kg (n=290)	Placebo (n=287)	Belimumab 1 mg/kg vs placebo		Belimumab 10 mg/kg vs placebo	
				Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
SRI response rate*	148 (51%)	167 (58%)	125 (44%)	1·55 (1·10 to 2·19)	0·0129	1·83 (1·30 to 2·59)	0·0006
Reduction ≥4 points in SELENA-SLEDAI†	153 (53%)	169 (58%)	132 (46%)	1·51 (1·07 to 2·14)	0·0189	1·71 (1·21 to 2·41)	0·0024
No worsening with BILAG‡	226 (78%)	236 (81%)	210 (73%)	1·38 (0·93 to 2·04)	0·1064	1·62 (1·09 to 2·42)	0·0181
No worsening with PGA	227 (79%)	231 (80%)	199 (69%)	1·68 (1·15 to 2·47)	0·0078	1·74 (1·18 to 2·55)	0·0048
Geographical region							
Asia-Pacific	42/111 (38%)	59/119 (50%)	42/109 (39%)	0·97 (0·56 to 1·67)	0·9156	1·57 (0·93 to 2·66)	0·0942
Latin America	85/143 (59%)	85/140 (61%)	71/145 (49%)	1·53 (0·96 to 2·43)	0·0750	1·61 (1·01 to 2·58)	0·0469
Eastern Europe	21/34 (62%)	23/31 (74%)	12/33 (36%)	2·83 (1·05 to 7·61)	0·0398	5·03 (1·72 to 14·70)	0·0032
Disease flares							
SFI, all							
Time to first flare during 52 weeks (days; median, range)§	126 (5–375)	119 (1–367)	84 (1–368)	0·75¶ (0·62 to 0·90)	0·0026	0·76¶ (0·63 to 0·91)	0·0036
Patients with flare	203 (70%)	205 (71%)	230 (80%)	..	..	..	..
SFI, severe							
Patients with flare	51 (18%)	40 (14%)	66 (23%)	0·76¶ (0·52 to 1·09)	0·1342	0·57¶ (0·39 to 0·85)	0·0055
BILAG							
New 1A or 2B	77 (27%)	54 (19%)	86 (30%)	0·89¶ (0·66 to 1·22)	0·4804	0·58¶ (0·41 to 0·81)	0·0016
New 1A	54 (19%)	29 (10%)	58 (20%)	0·88¶ (0·61 to 1·28)	0·4997	0·45¶ (0·28 to 0·70)	0·0004
PGA score							
Change (least square mean, SE) at week 24†	−0·39 (0·04)	−0·50 (0·04)	−0·35 (0·04)	−0·05‖ (−0·13 to 0·04)	0·2712	−0·15‖ (−0·23 to −0·07)	0·0003
Improvement (decrease ≥0·3) at week 52	169 (59%)	187 (64%)	141 (49%)	1·51 (1·08 to 2·11)	0·0147	1·88 (1·35 to 2·63)	0·0002
Steroid-sparing activity							
Prednisone dose reduced by ≥25% to ≤7·5 mg/day during weeks 40–52†	42/204 (21%)	38/204 (19%)	23/192 (12%)	1·89 (1·08 to 3·31)	0·0252	1·75 (0·99 to 3·08)	0·0526
Prednisone dose reduced by ≥50% at week 52	53/230 (23%)	64/231 (28%)	39/220 (18%)	1·39 (0·88 to 2·21)	0·1635	1·78 (1·13 to 2·79)	0·0122
Prednisone dose increased to >7·5 mg/day at week 52 from ≤7·5 mg/day	25/84 (30%)	17/86 (20%)	34/95 (36%)	0·82 (0·43 to 1·58)	0·5576	0·44 (0·22 to 0·88)	0·0196
Patients with sustained reduction (≥12 weeks)** in prednisone dose from a baseline of >7·5 mg/day	49/204 (24%)	57/204 (28%)	29/192 (15%)	1·60¶ (1·01 to 2·53)	0·0465	1·96¶ (1·25 to 3·07)	0·0032
Health-related quality of life (SF-36 PCS score, absolute change from baseline)							
Week 24 (least square mean, SE)†	3·39 (0·53)	3·34 (0·55)	3·26 (0·54)	0·13‖ (−0·95 to 1·21)	0·8127	0·08‖ (−1·00 to 1·15)	0·8870
Week 52 (least square mean, SE)	4·17 (0·58)	4·19 (0·60)	2·84 (0·60)	1·34‖ (0·15 to 2·52)	0·0272	1·35‖ (0·17 to 2·54)	0·0247
Biomarkers††							
Median (IQR) change in C3 concentration from baseline at week 52	2·74% (−9·38 to 16·33)	5·59% (−5·80 to 20·63)	−3·03% (−13·70 to 7·89)	..	0·0012	..	<0·0001
Return of low C3 concentrations to normal‡‡	27/119 (23%)	40/117 (34%)	14/99 (14%)	..	0·1046	..	0·0005
Median (IQR) change in C4 concentrations from baseline at week 52	21·83% (0 to 55·56)	30·38% (6·67 to 64·29)	0 (−14·29 to 23·81)	..	<0·0001	..	<0·0001
Return of low C4 concentrations to normal§§	51/141 (36%)	63/147 (43%)	23/119 (19%)	..	0·0024	..	<0·0001
Return of hypergammaglobulinaemia to normal	55/110 (50%)	64/131 (49%)	22/115 (19%)	..	<0·0001	..	<0·0001
Median (IQR) change in anti-dsDNA concentrations from baseline to week 52¶¶	−35·13% (−54·93 to −1·53)	−37·57% (−59·44 to −13·04)	−12·26% (−43·33 to 50·38)	..	<0·0001	..	<0·0001
Anti-dsDNA positive to negative at week 52	24/179 (13%)	31/182 (17%)	9/159 (6%)	..	0·0145	..	0·0008

Data are number (%) or n/N (%), unless otherwise indicated. p values are for pairwise comparison of the placebo group with the belimumab 1 mg/kg or 10 mg/kg group. SRI=Systemic Lupus Erythematosus Responder Index. SELENA-SLEDAI=Safety of Estrogens in Lupus Erythematosus National Assessment–Systemic Lupus Erythematosus Disease Activity Index. BILAG=British Isles Lupus Assessment Group. PGA=Physician's Global Assessment. SFI=Systemic Lupus Erythematosus Flare Index. SF-36 PCS=36-item Short-Form Health Survey physical component summary. C3=C3 complement. C4=C4 complement. *Percentage of patients with reduction in SELENA-SLEDAI score of at least 4, no worsening with BILAG index (no new 1A or 2B flares), and no worsening of PGA score (<0·3 increase) at week 52. †Major secondary endpoint. ‡No new BILAG 1A or 2B flares. §Mild-to-moderate or severe flare. ¶Hazard ratio. ‖Treatment difference. **Sustained prednisone reduction (≥12 weeks until week 52) of at least 50% or to less than 7·5 mg/day. ††Changes in concentrations of C3, C4, and anti-dsDNA were analysed by use of the Wilcoxon test, and the return of C3, C4, and hypergammaglobulinaemia to normal was analysed by use of a likelihood ratio test. Odds ratios were not applicable. ‡‡Low C3 concentration is less than 0·90 g/L. §§Low C4 concentration is less than 0·16 g/L. ¶¶Patients who were positive at baseline with anti-dsDNA (immunoglobulin G) assay with a detectable range of 30–3600 IU/mL.

Table 2: Results for primary and secondary endpoints
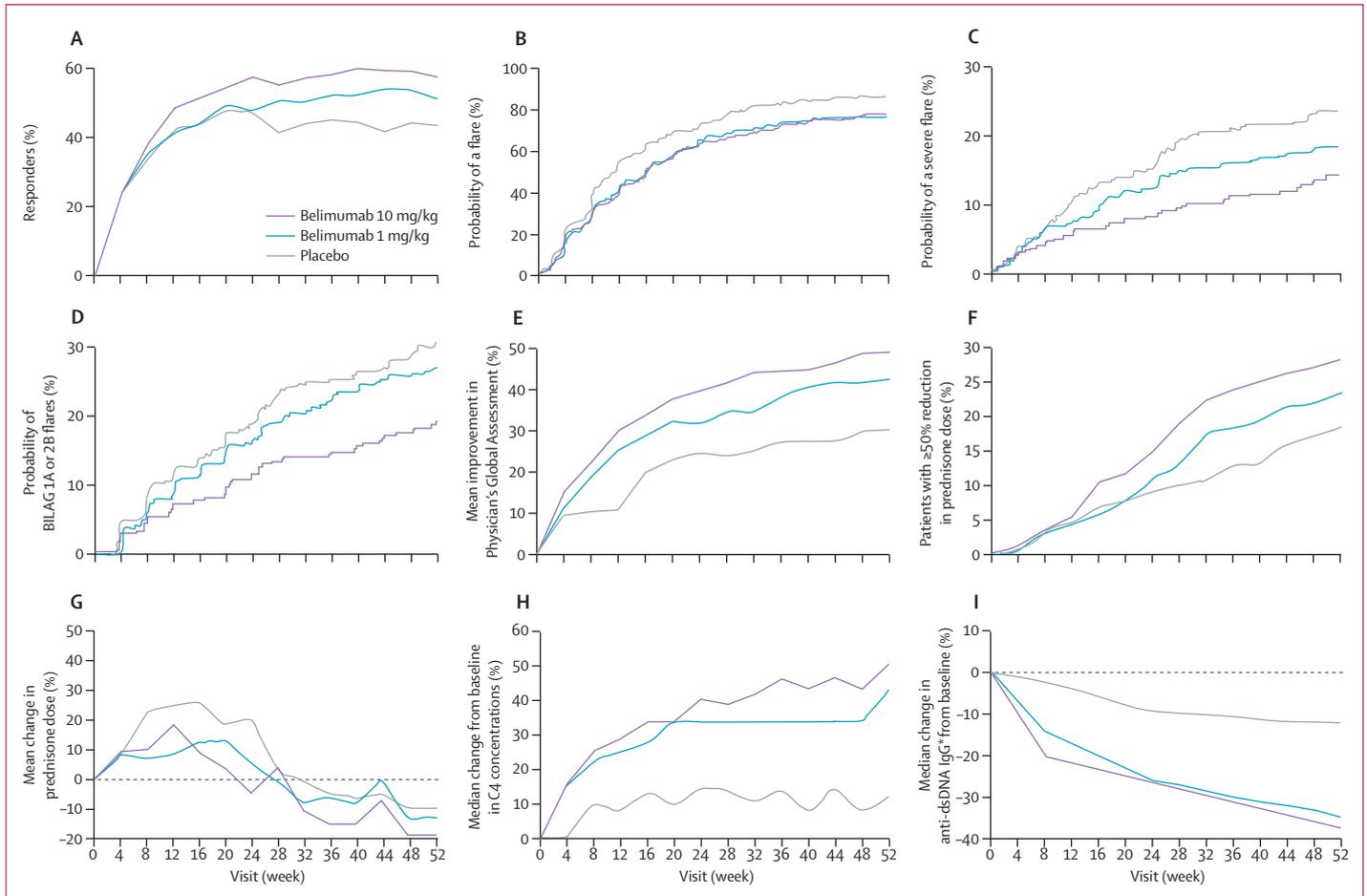
Figure 2: Results for primary efficacy endpoint and components
(A) Response to belimumab during 52 weeks assessed with the Systemic Lupus Erythematosus Responder Index. (B) Effect of belimumab on mild-to-moderate and severe flares assessed with the Safety of Estrogens in Lupus Erythematosus National Assessment–Systemic Lupus Erythematosus Disease Activity Index (modified flare index). (C) Effect of belimumab on severe flares only. (D) Effect of belimumab on British Isles Lupus Assessment Group (BILAG) organ domain flares (1A or 2B). (E) Improvement with belimumab assessed with the Physician's Global Assessment. (F) Effect of belimumab on steroid sparing (≥50% reduction). (G) Change in prednisone dose from baseline to 52 weeks. (H) Change in C4 complement concentrations from baseline in patients with low baseline concentrations. (I) Change in anti-dsDNA immunoglobulin G (IgG) from baseline to 52 weeks in patients with detectable anti-dsDNA at baseline. For (B), (C), and (D), Cox proportional hazard model was used to calculate p values for patients developing a flare during the 52 weeks of the study. *Dynamic range of the ELISA anti-dsDNA IgG test is 30–3600 IU/mL.

eastern Europe (36 [37%] of 98). Use of antimalarial drugs was less in eastern Europe (53 [54%] of 98) than in Latin America (294 [69%] of 428) and Asia-Pacific (234 [69%] of 339), but use of high-dose prednisone (>7·5 mg per day; 86 [88%] of 98) was greater than in Latin America (311 [73%] of 428) and Asia-Pacific (203 [60%] of 339).

When assessed with SRI, significantly more people showed a response in the belimumab 1 mg/kg and 10 mg/kg groups than in the placebo group at week 52 (table 2; figure 2A). Significantly greater responses were noted at each visit until week 52, starting at week 16 (but not including week 20) with belimumab 10 mg/kg and week 28 with belimumab 1 mg/kg (10 mg/kg: p=0·0486 at week 16, p=0·0112 at week 24, p=0·0008 at week 28, p=0·0013 at week 32, p=0·0013 at week 36, p=0·0001 at week 40, p<0·0001 at week 44, p=0·0002 at week 48, and p=0·0006 at week 52; 1 mg/kg: p=0·0074 at week 28,

p=0·0401 at week 32, p=0·0248 at week 36, p=0·0181 at week 40, p=0·0005 at week 44, p=0·0046 at week 48, and p=0·0129 at week 52; figure 2A). Significantly more patients in the belimumab groups achieved an improvement in the SELENA-SLEDAI score of at least 4 points at week 52 than in the placebo group (table 2). More patients treated with belimumab 1 mg/kg and 10 mg/kg had no disease worsening as assessed by no new BILAG A or no more than 1 new BILAG B organ domain score at week 52 than did those given placebo (table 2). Patients given belimumab were more likely to have stabilisation of disease—ie, no worsening in PGA score (<0·3 increase)—at week 52 than in the placebo group (table 2). Although the effect of belimumab was numerically greater in eastern Europe than in Asia-Pacific and Latin America, the difference between the three regions was not significant (p=0·18, treatment-by-region interaction for all treatments and regions).

The rate of disease flares was reduced and time to disease flares was increased during 52 weeks with belimumab, when assessed with SFI and new BILAG 1A or 2B organ domain scores (table 2; figure 2B–D). Improvement in the rate of SFI flares was noted as early as week 12 in the belimumab groups (figure 2B). The risk of developing any mild-to-moderate or severe SFI flare was reduced by 25% with belimumab 1 mg/kg and by 24% with belimumab 10 mg/kg compared with placebo (table 2; figure 2B). For patients given belimumab 10 mg/kg, the risks of developing a severe SFI flare, a new BILAG 1A or 2B organ domain flare, and a new BILAG A flare during 52 weeks were significantly reduced by 43%, 42%, and 55%, respectively, compared with the placebo group (table 2; figure 2C and D).

Belimumab 10 mg/kg resulted in a greater mean absolute reduction in PGA score, signifying improvement at week 24, than did placebo (table 2). By week 52, significantly more patients had a reduction of at least 0·3 in their PGA scores in the belimumab groups than in the placebo group (table 2). The percentage reductions in PGA from baseline were significantly greater as early as 8 weeks with belimumab 1 mg/kg, and 4 weeks with belimumab 10 mg/kg than with placebo; these differences were maintained throughout the 52 weeks (1 mg/kg: p=0·0199 at week 8, p=0·0010 at week 12, p=0·0063 at week 16, p=0·0092 at week 20, p=0·0342 at week 24, p=0·0073 at week 28, p=0·0110 at week 32, p=0·0059 at week 36, p=0·0013 at week 40, p=0·0004 at week 44, p=0·0032 at week 48, and p=0·0039 at week 52; 10 mg/kg: p=0·0489 at week 4, p=0·0008 at week 8, and p<0·0001 at weeks 12–52; figure 2E).

600 (69%) of 865 patients were taking prednisone at doses greater than 7·5 mg/day at baseline, and reductions in dose of at least 25% to 7·5 mg/day or less during weeks 40 to 52 were significantly greater with belimumab 1 mg/kg than with placebo (table 2). For the 265 (31%) patients on prednisone doses of 7·5 mg/day or less at baseline, significantly fewer increases to more than 7·5 mg/day at week 52 were noted with belimumab 10 mg/kg than with placebo, but not with belimumab 1 mg/kg (table 2). The proportions of patients with at least a 50% reduction in prednisone dose were significantly greater with belimumab 10 mg/kg at every visit from weeks 24 to 52 (10 mg/kg: p=0·0461 at week 24, p=0·0052 at week 28, p=0·0009 at week 32, p=0·0024 at week 36, p=0·0012 at week 40, p=0·0074 at week 44, p=0·0100 at week 48, and p=0·0122 at week 52; 1 mg/kg: p=0·0381 at week 32; figure 2F). For patients with baseline prednisone doses greater than 7·5 mg/day, the likelihood of a sustained dose reduction (≥12 weeks until week 52) was greater with belimumab 1 mg/kg and 10 mg/kg than with placebo (table 2). Use of prednisone was significantly greater in the placebo group than in the belimumab 10 mg/kg group from weeks 12 to 52 (p=0·0077 at week 12, p=0·0001 at week 16, p=0·0012 at week 20, p=0·0006 at week 24, p=0·0005 at week 28, p=0·0005 at week 32,

p=0·0005 at week 36, p=0·0003 at week 40, p=0·0010 at week 44, p=0·0017 at week 48, and p=0·0009 at week 52; figure 2G). In the first 16 weeks of the study, fewer than 2% of patients had a new antimalarial drug added to their treatment regimen or their dose of immunosuppressive drug increased, and none discontinued either types of these drugs. The number of patients who became treatment failures as a result of using restricted drugs at any time during the trial was higher in the placebo group (30 [10%] of 287) than in the belimumab 1 mg/kg (21 [7%] of 288; odds ratio 0·67 [95% CI 0·38–1·21]) and 10 mg/kg (18 [6%] of 290; 0·57 [0·31–1·04]) groups.

Although the treatment groups at week 24 did not differ significantly in the scores for SF-36 physical component summary, both belimumab groups had similar significant mean absolute increases at week 52 compared with placebo (table 2).

Both belimumab doses increased or returned complement concentrations to normal as early as week 4 (1 mg/kg: p<0·0001 at week 4, p=0·0011 at week 8, and p≤0·0001 at weeks 12–52; 10 mg/kg: p<0·0001 at weeks 4–52; figure 2H), reduced anti-dsDNA antibody concentrations as early as week 8, and resolved hypergammaglobulinaemia in a generally dose-dependent manner (1 mg/kg: p=0·0004 at week 8, p=0·0007 at week 24, and p<0·0001 at week 52; 10 mg/kg: p<0·0001 at week 8, p=0·0009 at week 24, and p<0·0001 at week 52; figure 2I). By week 52, significantly more patients converted from positive to negative for anti-dsDNA antibodies in the belimumab groups than in the placebo group (table 2).

During the 52 weeks of treatment and 8 weeks of follow-up, the occurrence of adverse events, serious or severe adverse events (including infections), laboratory abnormalities, and discontinuations due to adverse events (figure 1) were similar in the three groups (table 3). More than 90% of serious infections in all groups resulted in admission to hospital. No pattern was noted for the different types of infections in the three groups.

Infusion reactions were similar between groups (table 3). The rates of severe hypersensitivity or infusion reactions were numerically greater in the belimumab groups than in the placebo group (table 3). Three anaphylactic reactions were reported (two with belimumab 1 mg/kg and one with 10 mg/kg) after administration of the first dose; two cases were severe, with angioedema that resolved with prednisone or antihistamine drugs, and one was treated with epinephrine.

Nine patients died during the study (table 3). Three deaths in the belimumab groups were due to infections, and one patient in the placebo group died of cardiac arrest that was preceded by sepsis. No malignant diseases were reported.

Of 17 pregnancies with known outcomes, the rates of spontaneous abortion or stillbirth were similar in the three groups (table 3). Two stillbirths were reported after pre-eclampsia: one in the placebo group and one in the belimumab 10 mg/kg group.

	Belimumab 1 mg/kg (n=288)	Belimumab 10 mg/kg (n=290)	Placebo (n=287)
Adverse event (n≥1)	264 (92%)	266 (92%)	263 (92%)
Serious adverse event (n≥1)	47 (16%)	41 (14%)	36 (13%)
Severe adverse event (n≥1)	36 (13%)	33 (11%)	34 (12%)
Discontinuations due to adverse events	16 (6%)	15 (5%)	19 (7%)
Deaths	2 (<1%)*	4 (1%)	3 (1%)
Malignant neoplasm	0	0	0
Infections			
All	197 (68%)	194 (67%)	183 (64%)
Serious infection (n≥1)	22 (8%)	13 (4%)	17 (6%)
Severe infection (n≥1)†	10 (3%)	7 (2%)	9 (3%)
Admission to hospital due to infections	21 (7%)	11 (4%)	17 (6%)
Opportunistic infections	0	1 (<1%)‡	0
Treatment-emergent adverse events (≥10% of any treatment group)			
Headache	58 (20%)	66 (23%)	76 (26%)
Upper respiratory tract infection	41 (14%)	36 (12%)	47 (16%)
Arthralgia	21 (7%)	33 (11%)	34 (12%)
Urinary tract infection	30 (10%)	26 (9%)	25 (9%)
Influenza	22 (8%)	33 (11%)	25 (9%)
Diarrhoea	28 (10%)	30 (10%)	20 (7%)
Nasopharyngitis	30 (10%)	20 (7%)	23 (8%)
Hypertension	25 (9%)	17 (6%)	30 (10%)
Nausea	16 (6%)	23 (8%)	31 (11%)
Infusion reactions§			
All (including hypersensitivity)	47 (16%)	48 (17%)	49 (17%)
Requiring medical intervention¶	21 (7%)	25 (9%)	24 (8%)
Severe	3 (1%)	4 (1%)	1 (<1%)
Laboratory abnormalities of grade 3 or 4 in >2% of patients given belimumab 10 mg/kg			
White blood cells (<2×10⁹ L)	3 (1%)	12 (4%)	10 (3%)
Neutrophils (<1×10⁹ L)	11 (4%)	11 (4%)	11 (4%)
Lymphocytes (<5×10⁸ L)	80 (28%)	75 (26%)	73 (25%)
Haemoglobin (≤80 g/L)	12 (4%)	5 (2%)	14 (5%)
Prothrombin time (17·25 s) ‖	17 (6%)	16 (6%)	12 (4%)
Proteinuria (>2 g/24 h)**	47 (16%)	40 (14%)	51 (18%)
Hypogammaglobulinaemia (<4 g/L)††	0	1 (<1%)‡‡	0
Median (IQR) change in Ig from baseline§§			
IgG	−14·1% (−24·49 to −5·44)	−15·6% (−23·92 to −6·64)	−3·6% (−14·50 to 6·10)
IgA	−16·8% (−24·42 to −8·04)	−16·0% (−25·11 to −7·17)	−2·7% (−13·35 to 8·68)
IgM	−28·5% (−41·51 to −18·18)	−30·0% (−40·00 to −19·47)	−3·2% (−14·87 to 11·84)
Pregnancy			
All	4 (1%)	11 (4%)	5 (2%)
Spontaneous abortion or stillbirth¶¶	1/3 (33%)	5/9 (56%)	3/5 (60%)

Data are number (%) or n/N (%), unless otherwise indicated. Ig=immunoglobulin. *One additional systemic lupus erythematosus-related death occurred >15 weeks past the last belimumab dose and discontinuation from the study. †Grades 3 and 4. ‡Sepsis caused by *Acinetobacter baumannii* occurred on day 16 in the group assigned to belimumab 10 mg/kg and was judged to be an opportunistic infection; a second case that was not coded (*Acinetobacter wolfii* pneumonia) on day 0 was identified in the group assigned to 1 mg/kg; both patients completely recovered with antibiotics. There was no report of tuberculosis. §Infusion reactions that occurred on the day of an infusion and resolved within 7 days, and all hypersensitivity reactions that occurred on the day of infusion; these included three cases of anaphylactic reactions (two severe and one mild), all of which resolved on the day of reaction to treatment. ¶Study treatment interrupted or discontinued or drug given. ‖19 (58%) of 33 patients given belimumab and ten (83%) of 12 in the placebo group with grades 3 and 4 prothrombin time were taking warfarin. **Assessed by use of spot urine protein-to-creatinine ratio. ††Grade 3 is IgG concentration less than 4 g/L; grade 4 is IgG concentration less than 2·5 g/L. ‡‡One patient had grade 2 IgG hypergammaglobulinaemia at baseline. §§IgG collected at weeks 8, 24, 40, and 52, and IgM and IgA at week 52. ¶¶Results based on patients with known outcomes.

Table 3: Treatment-emergent adverse events and pregnancy outcomes during 52 weeks of study

The incidence of grade 3 or 4 laboratory abnormalities did not differ between the three groups (table 3). Reductions from baseline in concentrations of IgG, IgM, and IgA were significantly (p<0·0001) greater in the belimumab 1 mg/kg and 10 mg/kg groups than in the placebo group (table 3). Only a few patients had IgG concentrations that were less than normal at baseline and at week 52 in all groups, but the concentrations were slightly higher in the belimumab groups (placebo: one [<1%] of 287 and one [<1%] of 225, respectively; belimumab 1 mg/kg: none of 288 and five [2%] of 239, respectively; and belimumab 10 mg/kg: three [1%] of 290 and six [2%] of 243, respectively). No severe infections were associated with severe neutropenia or hypo-gammaglobulinaemia.

Discussion

Belimumab with standard of care resulted in a significantly higher response rate than did placebo and standard of care at week 52 when assessed with SRI. A dose-response pattern was noted, with belimumab 10 mg/kg resulting in a significantly greater response than did placebo in all three SRI components, whereas belimumab 1 mg/kg resulted in a greater response than did placebo in two components (SELENA-SLEDAI and PGA).

The onset of clinical improvement with belimumab, assessed with SRI and flare reduction, was noted as early as week 16, when the 10 mg/kg group first showed significant improvement with SRI and SELENA-SLEDAI.[19,31,34,35] Improvement in PGA with belimumab occurred by weeks 4–8 and was maintained until week 52. The overall reduction in risk of flares with belimumab was shown by the increases in median time to any flare in both belimumab groups compared with the placebo group. Furthermore, the risk of moderate-to-severe flares when assessed with BILAG, and occurrence of clinically meaningful severe flares as assessed with both SFI and BILAG, were significantly reduced in the belimumab 10 mg/kg group. Additionally, health-related quality of life, assessed with the score for SF-36 physical component summary, was significantly improved in both belimumab groups at week 52, and patients with an SRI response had a better score for the physical component summary than did those who did not respond. A reduction in the occurrence of flares is likely to reduce long-term damage, morbidity, and mortality, resulting in improved patient outcomes with reduced disease costs and improved health-related quality of life.[36,37]

Belimumab resulted in a rapid, selective, and sustained improvement in serological activity. As early as 8 weeks after initiation of belimumab, significantly greater reductions were noted in concentrations of anti-dsDNA, which were sustained until week 52. The reduction in anti-dsDNA concentrations was much greater than the overall reduction in IgG concentrations in patients who were positive for anti-dsDNA at baseline. Additionally, significantly more patients treated with belimumab had

their hypergammaglobulinaemia and low complement concentrations returned to normal. These findings are consistent with the mechanism of action of belimumab, which results in reduced BLyS concentrations and thereby allows autoimmune B cells to undergo apoptosis, preventing escape and proliferation of new or existing autoimmune B-cell clones.[8,9]

Belimumab also had steroid-sparing effects, as shown by the higher average prednisone dose in the placebo group than in the belimumab groups from week 8 and significant reductions in prednisone use in the belimumab groups compared with the placebo group during the last 36 weeks of the study. In patients taking prednisone at a dose greater than 7·5 mg/day at baseline, the likelihood of a sustained dose reduction with belimumab versus placebo was dose-dependently greater. Fewer patients in both belimumab groups needed a prednisone dose increase greater than 7·5 mg/day during the trial than in the placebo group. Prolonged high doses of corticosteroids are the main cause of long-term damage and morbidity in patients with systemic lupus erythematosus.[38,39] Reduction in steroid dose, therefore, has clinical significance for prevention of side-effects and long-term damage, reduction of the risk of infection, and improvement of the general health of patients with systemic lupus erythematosus.[37] Additionally, fewer patients on belimumab became treatment failures as a result of the use of protocol-prohibited concomitant drugs during the study.

Several lessons learned from the phase 2 trial of patients with systemic lupus erythematosus were applied to the design of this phase 3 study. First, patients with serological activity that was indicative of B-cell hyperactivity were selected. Second, use of SRI as the primary efficacy endpoint optimised the strengths of the disease activity scales. Third, the study was designed to require fairly stable (but active) disease activity without the need for induction with high-dose steroids at entry. Fourth, investigators were given extensive training and testing in terms of assessment of disease activity and flare. Fifth, progressively stricter control of concurrent drugs that might improve disease activity and reduce the effect of belimumab compared with placebo was imposed during the last 2–6 months of the study.

Importantly, with respect to the limitations of this study, rare safety signals cannot be ruled out until a much larger number of patients is treated with belimumab for longer than 52 weeks. The BLISS-52 trial design prevented direct comparison with any specific standard of care and assessment of patient subgroups excluded from the trial (eg, paediatric, severe active lupus nephritis, and CNS vasculitis).

Both doses of belimumab had a safety profile similar to that of placebo, with no significant differences between treatment groups in the occurrence of serious adverse events—infections, deaths, malignant diseases, spontaneous abortions, stillbirths, laboratory abnor-malities, or discontinuations attributable to adverse

events. Severe hypersensitivity infusion reactions were not common and were reversible with standard treatment. 20 pregnancies were reported despite strict protocol provisions to avoid conception; the 17 known outcomes of these pregnancies were not different among the three treatment groups.

In conclusion, the results of this phase 3 trial showed the safety profile and efficacy of belimumab in controlling systemic lupus erythematosus in a broad range of patients. Inhibition of soluble BLyS with belimumab represents a new path forward in the management of this important autoimmune disease.

References
1 Rahman A, Isenberg DA. Systemic lupus erythematosus. *N Engl J Med* 2008; **358:** 929–39.

2 Bernatsky S, Boivin J-F, Joseph L, et al. Mortality in systemic lupus erythematosus. *Arthritis Rheum* 2006; **54:** 2550–57.

3 Cervera R, Khamashta MA, Font J, et al. Morbidity and mortality in systemic lupus erythematosus during a 10-year period: a comparison of early and late manifestations in a cohort of 1,000 patients. *Medicine* 2003; **82:** 299–308.

4 Doria A, Canova M, Tonon M, et al. Infections as triggers and complications of systemic lupus erythematosus. *Autoimmun Rev* 2008; **8:** 24–28.

5 Campbell R Jr, Cooper GS, Gilkeson GS. Two aspects of the clinical and humanistic burden of systemic lupus erythematosus: mortality risk and quality of life early in the course of disease. *Arthritis Rheum* 2008; **59:** 458–64.

6 Thumboo J, Strand V. Health-related quality of life in patients with systemic lupus erythematosus: an update. *Ann Acad Med Singapore* 2007; **36:** 115–22.

7 Moore PA, Belvedere O, Orr A, et al. BLyS: member of the tumor necrosis factor family and B lymphocyte stimulator. *Science* 1999; **285:** 260–63.

8 Cancro MP, D'Cruz DP, Khamashta MA. The role of B lymphocyte stimulator (BLyS) in systemic lupus erythematosus. *J Clin Invest* 2009; **119:** 1066–73.

9 Mackay F, Schneider P. Cracking the BAFF code. *Nat Rev Immunol* 2009; **9:** 491–502.

10 Cheema GS, Roschke V, Hilbert DM, Stohl W. Elevated serum B lymphocyte stimulator levels in patients with systemic immune-based rheumatic diseases. *Arthritis Rheum* 2001; **44:** 1313–19.

11 Mariette X, Roux S, Zhang J, et al. The level of BLyS (BAFF) correlates with the titre of autoantibodies in human Sjögren's syndrome. *Ann Rheum Dis* 2003; **62:** 168–71.

12 Zhang J, Roschke V, Baker KP, et al. Cutting edge: a role for B lymphocyte stimulator in systemic lupus erythematosus. *J Immunol* 2001; **166:** 6–10.

13 Collins CE, Gavin AL, Migone T-S, Hilbert DM, Nemazee D, Stohl W. B lymphocyte stimulator (BLyS) isoforms in systemic lupus erythematosus: disease activity correlates better with blood leukocyte BLyS mRNA levels than with plasma BLyS protein levels. *Arthritis Res Ther* 2006; **8:** R6.

14 Petri M, Stohl W, Chatham W, et al. Association of plasma B-lymphocyte stimulator (BLyS) levels and disease activity in systemic lupus erythematosus. *Arthritis Rheum* 2008; **58:** 2453–59.

15 Baker KP, Edwards BM, Main SH, et al. Generation and characterization of LymphoStat-B, a human monoclonal antibody that antagonizes the bioactivities of B lymphocyte stimulator. *Arthritis Rheum* 2003; **48:** 3253–65.

16 Halpern WG, Lappin P, Zanardi T, et al. Chronic administration of belimumab, a BLyS antagonist, decreases tissue and peripheral blood B-lymphocyte populations in cynomolgus monkeys: pharmacokinetic, pharmacodynamic, and toxicologic effects. *Toxicol Sci* 2006; **91:** 586–99.

17 Wallace DJ, Stohl W, Furie RA, et al. A phase II, randomized, double-blind, placebo-controlled, dose-ranging study of belimumab in patients with active systemic lupus erythematosus. *Arthritis Rheum* 2009; **61:** 1168–78.

18 Petri M, Furie R, Merrill J, et al. Four-year experience of belimumab, a BLyS specific inhibitor, in systemic lupus erythematosus (SLE) patients. *Arthritis Rheum* 2009; **60** (suppl 10)**:** S774. 2069 (abstr).

19 Furie RA, Petri MA, Wallace DJ, et al. Novel evidence-based systemic lupus erythematosus responder index. *Arthritis Rheum* 2009; **61:** 1143–51.

20 Kalunian K, Merrill JT. New directions in the treatment of systemic lupus erythematosus. *Curr Med Res Opin* 2009; **25:** 1501–14.

21 Strand V. Lessons learned from clinical trials in SLE. *Autoimmun Rev* 2007; **6:** 209–14.

22 US Food and Drug Administration. Guidance for industry: systemic lupus erythematosus—developing drugs for treatment. 2005. http://www.fda.gov/downloads/Drugs/GuidanceCompliance RegulatoryInformation/Guidances/ucm072063.pdf (accessed Feb 15, 2010).

23   Bertsias G, Gordon C, Boumpas DT. Clinical trials in systemic lupus erythematosus (SLE): lessons from the past as we proceed to the future—the EULAR recommendations for the management of SLE and the use of end-points in clinical trials. *Lupus* 2008; **17:** 437–42.

24   Dall'Era M, Wofsy D. Systemic lupus erythematosus clinical trials: an interim analysis. *Nat Rev Rheumatol* 2009; **5:** 348–51.

25   Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997; **40:** 1725.

26   Petri M, Kim MY, Kalunian KC, et al. Combined oral contraceptives in women with systemic lupus erythematosus. *N Engl J Med* 2005; **353:** 2550–58.

27   Petri M, Buyon J, Kim M. Classification and definition of major flares in SLE clinical trials. *Lupus* 1999; **8:** 685–91.

28   Hay EM, Bacon PA, Gordon C, et al. The BILAG index: a reliable and valid instrument for measuring clinical disease activity in systemic lupus erythematosus. *Q J Med* 1993; **86:** 447–58.

29   Isenberg DA, Gordon C. From BILAG to BLIPS—disease activity assessment in lupus past, present and future. *Lupus* 2000; **9:** 651–54.

30   Ware JE, Kosinski M. The SF-36 health survey (version 2.0) technical note. Boston, MA: Health Assessment Lab, 1997.

31   Gladman DD, Urowitz MB, Kagal A, Hallett D. Accurately describing changes in disease activity in systemic lupus erythematosus. *J Rheumatol* 2000; **27:** 377–79.

32   Gordon C, Sutcliffe N, Skan J, Stoll T, Isenberg DA. Definition and treatment of lupus flares measured by the BILAG index. *Rheumatology (Oxford)* 2003; **42:** 1372–79.

33   Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH. Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. *Arthritis Rheum* 1992; **35:** 630–40.

34   Ho A, Madger LS, Barr SG, Petri M. Decreases in anti-double stranded DNA levels are associated with concurrent flares in patients with systemic lupus erythematosus. *Arthritis Rheum* 2001; **44:** 2342–49.

35   Yee CS, Farewell V, Isenberg DA, et al. British Isles Lupus Assessment Group 2004 index is valid for assessment of disease activity in systemic lupus erythematosus. *Arthritis Rheum* 2007; **56:** 4113–19.

36   Bertsias G, Ioannidis JPA, Boletis J, et al. EULAR recommendations for the management of systemic lupus erythematosus. Report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics. *Ann Rheum Dis* 2008; **67:** 195–205.

37   Zhu TY, Tam LS, Lee VW, Lee KK, Li EK. The impact of flare on disease costs of patients with systemic lupus erythematosus. *Arthritis Rheum* 2009; **61:** 1159–67.

38   Zonana-Nacach A, Barr SG, Magder LS, Petri M. Damage in systemic lupus erythematosus and its association with corticosteroids. *Arthritis Rheum* 2000; **43:** 1801–08.

39   Chatham WW, Kimberly RP. Treatment of lupus with corticosteroids. *Lupus* 2001; **10:** 140–47.

APPLICABLE TO U.S. HEALTHCARE PROFESSIONALS AND U.S. HEALTHCARE ORGANIZATIONS ONLY

Under the U.S. Physician Payment Sunshine Act (Section 6002 of the Patient Protection and Affordable Care Act), beginning August 1, 2013 applicable manufacturers (including GlaxoSmithKline [GSK]) and group purchasing organizations are required to report all payments and transfers of value to healthcare professionals and healthcare organizations to the Centers for Medicare and Medicaid Services (CMS). In some circumstances, this may also apply to U.S. healthcare professionals residing outside of the U.S.

CMS considers fulfillment of articles for which GSK pays copyright to be a transfer of value and therefore will be included in the disclosure report. These reports can be found at http://fortherecord.payments.us.gsk.com/. Information about these reports can be found on this website or by contacting the GSK Customer Response Center at 1-888-725-0016 during the hours of Monday through Friday from 8:30 AM to 5:30 PM Eastern Time.