Lupus (2013) 22, 144–154
http://lup.sagepub.com

PAPER

Safety profile of belimumab: pooled data from placebo-controlled phase 2 and 3 studies in patients with systemic lupus erythematosus

DJ Wallace[1], S Navarra[2], MA Petri[3], A Gallacher[4], M Thomas[5], R Furie[6], RA Levy[7], RF van Vollenhoven[8], S Cooper[9], ZJ Zhong[9], W Freimuth[9] and R Cervera[10], for the BLISS-52 and -76, and LBSL02 Study Groups
[1]Cedars-Sinai Medical Center/David Geffen School of Medicine at UCLA, Los Angeles, California, USA; [2]University of Santo Tomas Hospital, Manila, Philippines; [3]Johns Hopkins University, Baltimore, Maryland, USA; [4]Hospital Británico de Buenos Aires, Argentina; [5]Kerala Institute of Medical Sciences, Trivandrum, Kerala, India; [6]North Shore–LIJ Health System, Lake Success, New York, USA; [7]Hospital Universitário Pedro Ernesto, UERJ, Rio de Janeiro, Brazil; [8]The Karolinska Institute, Stockholm, Sweden; [9]Human Genome Sciences, Inc., Rockville, Maryland, USA; and [10]Hospital Clinic, Barcelona, Catalonia, Spain

Safety data were pooled and analyzed from one phase 2 and two phase 3 double-blind, placebo-controlled, repeat-dose systemic lupus erythematosus (SLE) trials of belimumab 1, 4 (phase 2 only), and 10 mg/kg. Types and rates of adverse events (AEs) were similar across treatment groups. Rates of patients experiencing any serious AE were 16.6%, 19.5%, 13.5%, and 18.0% with placebo, and belimumab 1, 4, and 10 mg/kg, respectively; rates of serious infusion reactions (including hypersensitivity reactions) occurring on the same days as infusions were 0.4%, 0.9%, 0%, and 0.9%, and rates of serious infections were 5.5%, 7.1%, 6.3%, and 5.3%. Malignancy rates/100 patient-years (excluding non-melanoma skin cancer) were 0.29 with placebo vs. 0.20 with all belimumab doses combined; mortality rates/100 patient-years were 0.43 vs. 0.73. These data support the conclusion that belimumab in combination with standard SLE therapy was generally well tolerated in a predominantly autoantibody-positive population with active SLE. **ClinicalTrials.gov identifiers**: LBSL02: NCT00071487; BLISS-52: NCT00424476; BLISS-76: NCT00410384. *Lupus* (2013) **22,** 144–154.

Key words: Belimumab; safety; systemic lupus erythematosus

Background

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disorder characterized by autoantibody production, abnormal lymphocyte function, and chronic inflammation.[1,2] Despite improvements in survival in recent decades, SLE remains associated with significant mortality stemming, in part, from an increased risk of death from infection, heart disease, or certain malignancies, particularly hematologic cancers (e.g. non-Hodgkin's lymphoma) and lung cancer. Standard SLE therapies may contribute to these risks.[3–6] Systemic lupus erythematosus results in poorer health-related quality of life compared with the general population.[4,7]

Belimumab is a human immunoglobulin (Ig)-G1λ monoclonal antibody that inhibits the survival of autoreactive B cells by preventing the B-cell survival factor, B-lymphocyte stimulator (BLyS), from binding to its receptors on B cells.[1] Binding of BLyS to B cells during late stages of B-cell maturation is required for these cells to survive and undergo further differentiation. Autoreactive B cells are particularly dependent on soluble BLyS for survival and are generally eliminated in an environment with low BLyS levels; however, in a milieu with high BLyS levels, these cells may bind BLyS and survive.[8,9] Elevated serum levels of soluble BLyS protein correlate with SLE disease activity.[10]

Two phase 3 trials – BLISS-52 and BLISS-76 – demonstrated a significantly greater proportion of responders (using the SLE Responder Index)

Correspondence to: Daniel J Wallace, Cedars-Sinai Medical Center/David Geffen School of Medicine at UCLA, 8737 Beverly Blvd, Suite 302, W Hollywood, California 90048, USA.
Email: dwallace@ucla.edu
Received 27 April 2012; accepted 5 November 2012

10.1177/0961203312469259

treated with belimumab plus standard SLE therapy than with placebo plus standard therapy.[11,12] This analysis presents pooled safety data from these phase 3 trials and also the phase 2 double-blind trial.[11–13]

Patients and methods

In all, 1458 patients were exposed to belimumab 1, 4, or 10 mg/kg during the phase 2 and 3 clinical trials. The safety data presented are derived from the randomized controlled portions of the three trials, as well as an 8-week follow-up visit for patients who dropped out before trial completion or chose not to participate in the continuation studies. The long-term extension studies for patients who satisfactorily completed these trials are ongoing and not included in this analysis, except for pregnancy data, which includes long-term extension data through 31 December 2010.

Analyses were performed on data from the modified intention-to-treat population, meaning the subset of all randomized patients who received at least one dose of belimumab, in the three double-blind, controlled, repeat-dose SLE trials, unless otherwise specified.

Study designs

The phase 2 double-blind study ($N = 449$ randomized) was conducted at 59 sites in the United States and Canada, and included patients with active SLE (defined as a score ≥ 4 on the Safety of Estrogens in Lupus Erythematosus National Assessment–SLE Disease Activity Index [SELENA-SLEDAI]).[13] Patients were randomized to receive either placebo, or belimumab 1, 4, or 10 mg/kg for 52 weeks, plus standard therapy. The belimumab 4-mg/kg dose was administered only in the phase 2 trial; therefore, the safety of this dose can only be evaluated within the context of that study (as reported by Wallace et al).[13]

BLISS-52 ($N = 865$) enrolled patients from 90 centers in 13 countries in Latin America, the Asia-Pacific region, and Eastern Europe; BLISS-76 ($N = 819$) enrolled patients from 136 centers in 19 countries in Europe and North/Central America.[11,12] The enrollment criteria for the two trials included patients with active SLE (defined as a score ≥ 6 on SELENA-SLEDAI) who were autoantibody-positive, on stable standard therapy for ≥ 30 days, and without severe active lupus nephritis or central nervous system lupus. Patients were randomized to receive placebo, or belimumab 1 or 10 mg/kg, plus standard therapy, for 52 (BLISS-52) or 76 (BLISS-76) weeks.

Institutional review boards or ethics committees at each institution reviewed and approved the respective studies.[11–13] All patients signed informed consent forms. Studies were conducted in compliance with the International Conference on Harmonisation Guideline for Good Clinical Practice, in accordance with the principles for protecting human subjects originating in the Helsinki Declaration. Data safety monitoring was performed by independent external data monitoring committees.

In the belimumab clinical program, certain adverse events (AEs) of special interest were prespecified and monitored: infusion and hypersensitivity reactions, infections, and malignancies.[11–13] Infusion reactions were defined as any of a predetermined set of Medical Dictionary for Regulatory Activities preferred terms that occurred on the day of an infusion (and resolved within 7 days), plus hypersensitivity reactions. The prespecified group of terms defining infusion reactions was broad and included AEs that perhaps would not be considered classic infusion reactions (e.g. headache, nausea, and arthralgia).

Results

Baseline characteristics and concomitant medications

Baseline revised American College of Rheumatology SLE classification criteria, as well as patient and disease characteristics, were similar across treatment groups (Table 1).[14] Of the 11 criteria comprising this classification, 98% of patients were antinuclear antibody positive, 90% had arthritis, 76% had an immunologic disorder, 71% had malar rash, 69% had photosensitive rash, 54% had a hematologic disorder, 51% had oral or nasal ulcer, 30% had a renal disorder, 23% had discoid rash, and 6% had seizure or psychosis. The majority of patients were receiving ≥ 2 concomitant SLE medications. The most common concomitant medications used in these patients were as follows: corticosteroids (83%), antimalarials (66%), immunosuppressives (49%), non-steroidal anti-inflammatory drugs (35%), and angiotensin pathway antihypertensives (23%).

The average baseline doses of corticosteroids, and the proportions of patients receiving any corticosteroids and >7.5-mg/d doses are provided in Table 1. Changes in corticosteroid use during the course of the phase 2 and 3 trials were reported in

Table 1 Baseline demographics and disease characteristics

	Standard therapy +			
	Placebo ($n=675$)	Belimumab 1 mg/kg ($n=673$)	Belimumab 4 mg/kg[a] ($n=111$)	Belimumab 10 mg/kg ($n=674$)
Mean age ± SD, y	38.8 ± 11.9	38.2 ± 11.5	42.6 ± 10.7	38.5 ± 11.4
Woman, %	92.4	93.8	94.6	95.5
Race, %				
Caucasian	51.9	52.0	68.5	50.1
Asian	17.8	17.1	0.9	19.4
Black	11.0	10.7	27.9	11.6
Hispanic/Latino origin, %	32.4	32.7	21.6	31.6
Alaska Native or American Indian from North/Central/South America, %	19.0	20.1	2.7	18.7
Native Hawaiian or other Pacific Islander, %	0.4	0.1	0	0.1
Region, %				
US/Canada	38.2	40.0	100.0	36.6
Americas, excluding US/Canada	25.9	25.1	0	25.5
Asia	15.3	15.8	0	17.1
Western Europe/Australia/Israel	10.4	10.1	0	11.7
Eastern Europe	10.2	9.1	0	9.1
Baseline disease activity				
Mean SLE disease duration, y	6.9 ± 6.7	6.8 ± 6.4	10.1 ± 9.2	6.5 ± 6.8
Mean SELENA-SLEDAI score ± SD	9.7 ± 4.1	9.7 ± 3.9	9.4 ± 4.7	9.7 ± 3.8
Score ≥10, %[b]	53.0	52.8	51.9	51.9
Mean PGA score ± SD	1.5 ± 0.5	1.5 ± 0.5	1.5 ± 0.5	1.4 ± 0.5
BILAG organ involvement, %				
≥1 A or ≥2 B scores	62.5	62.1	64.9	61.7
≥1 A score	16.3	17.2	18.9	14.2
Mean SLICC Damage Index ± SD[c]	0.8 ± 1.2	0.8 ± 1.3	–	0.7 ± 1.2
Proteinuria (≥2 g/24 h)[b]	6.0	5.7	2.7	6.4
ANA ≥1:80, %	89.0	90.5	74.5	88.3
Anti-dsDNA ≥30 IU/mL, %	64.7	67.0	47.7	66.8
Mean IgG (g/L) ± SD	16.1 ± 6.1	16.1 ± 6.4	13.9 ± 5.1	16.0 ± 5.9
>16.2 g/L, %	41.9	41.3	29.7	40.8
Mean IgA (g/L) ± SD	3.1 ± 1.5	3.1 ± 1.5	2.8 ± 1.6	3.1 ± 1.5
Mean IgM (g/L) ± SD	1.1 ± 0.8	1.1 ± 0.7	1.3 ± 1.0	1.2 ± 0.8
Low C3 (<90 mg/dL)	41.0	42.8	27.9	44.1
Low C4 (<16 mg/dL)	51.1	54.5	36.9	55.0
Baseline medication use				
Glucocorticoid use, %	84.4	84.0	65.8	81.8
Mean dose ± SD, mg/kg (prednisone or equivalent)	10.5 ± 8.8	10.2 ± 8.5	7.0 ± 9.9	10.2 ± 9.2
>7.5 mg/d, % (prednisone or equivalent)	54.7	56.2	31.5	53.6
Antimalarial use, %	69.0	66.3	64.9	63.8
Other immunosuppressants, %	49.0	48.3	53.2	48.7
Azathioprine	21.6	20.7	20.7	24.2
Methotrexate	16.0	14.1	18.0	11.3
Mycophenolate mofetil	10.7	11.3	14.4	11.7

ANA: antinuclear antibody; anti-dsDNA: anti-double-stranded DNA; BILAG: British Isles Lupus Assessment Group; C: complement; PGA: Physician Global Assessment; SD: standard deviation; SELENA-SLEDAI: Safety of Estrogens in Lupus Erythematosus National Assessment–Systemic Lupus Erythematosus Disease Activity Index; SLE: systemic lupus erythematosus; SLICC: Systemic Lupus International Collaborating Clinics.

[a]The belimumab 4-mg/kg dose was administered only in the phase 2 trial; therefore, the safety of this dose can only be evaluated within the context of that study (as reported by Wallace et al[13]).

[b]Stratification factors used in phase 3 studies only: placebo, $n=562$; 1 mg/kg, $n=559$; 10 mg/kg, $n=563$.

[c]SLICC Damage Index score was not collected in the phase 2 trial.

Table 2 Patient disposition

	Standard therapy +			
	Placebo ($n=675$), %	Belimumab 1 mg/kg ($n=673$), %	Belimumab 4 mg/kg[a] ($n=111$), %	Belimumab 10 mg/kg ($n=674$), %
Completed placebo-controlled period	74.8	78.2	84.7	77.4
Withdrawn during placebo-controlled period	25.2	21.8	15.3	22.6
AE	7.0	6.2	3.6	6.8
Patient request	6.1	5.1	6.3	4.5
Disease progression/lack of efficacy	5.5	3.9	0	4.5
Protocol violation	1.9	1.2	0	1.3
Lost to follow-up	1.2	1.8	0	1.3
Lack of compliance	1.3	0.9	2.7	0.9
Investigator decision	0.9	0.7	0	1.0
Other	1.3	2.1	2.7	2.2
Pregnancy[b]	0.9	2.5	0.1	3.1

AE: adverse event.
[a]The belimumab 4-mg/kg dose was administered only in the phase 2 trial; therefore, the safety of this dose can only be evaluated within the context of that study (as reported by Wallace et al[13]).
[b]As of December 31, 2010; includes data from 1158 patients treated with belimumab 10 mg/kg in the phase 2 and 3 placebo-controlled periods of the phase 2 and 3 trials, and the respective extension studies (note: additional pregnancies may not have been listed as "withdrawals due to pregnancy," but rather as AEs using Medical Dictionary for Regulatory Activities codes for pregnancy, withdrawals due to investigator decisions, or as cases of spontaneous abortions or pregnancy lost to follow-up).

the original manuscripts detailing the primary safety and efficacy results.[11–13] In all three trials, there was indication of corticosteroid sparing with belimumab treatment compared with standard SLE therapy alone.

Study drug exposure and patient disposition

Of the 1458 patients who received at least one dose of belimumab 1, 4, or 10 mg/kg during the double-blind phases of the three trials, 78.3% completed the trial period (Table 2). Adverse events were the most common reason for withdrawal, with similar rates across treatment groups. The types of AEs most frequently leading to treatment discontinuations were renal disorders (1.2%, 0.9%, 0%, and 1.2% with placebo, and belimumab 1, 4, and 10 mg/kg, respectively), infections (1.2%, 0.7%, 0.9%, and 0.6%), neurologic disorders (0.6%, 0.7%, 0%, and 1.0%), and skin disorders (0.9%, 0.4%, 0.9%, and 0.7%). The most frequent AEs leading to discontinuation occurring in ≥5 patients across all treatment groups were lupus nephritis (1.2%, 0.6%, 0%, and 0.9% with placebo, and belimumab 1, 4, and 10 mg/kg, respectively) and infusion-related reactions (0.1%, 0.3%, 0%, and 0.7%).

Incidence of adverse events

Table 3 lists incidence rates of overall AEs, severe and serious AEs, deaths, most common AEs, and AEs of special interest. More than 90% of patients had at least one AE, with similar rates across treatment groups. Most AEs were mild or moderate in severity. Treatment groups did not differ in the incidence of overall AEs, treatment-related AEs, severe or serious AEs, or AEs resulting in treatment discontinuations.

The rates of serious AEs were 16.6%, 19.5%, 13.5%, and 18.0% with placebo, and belimumab 1, 4, and 10 mg/kg, respectively. The most common serious AEs (i.e. those occurring in ≥1% of patients in any treatment group) were pneumonia, urinary tract infection, lupus nephritis, pyrexia, and cellulitis. Serious cases of pyrexia (1.3% vs. 0.4%) and anemia (0.9% vs. 0.3%) occurred more frequently with belimumab 10 mg/kg vs placebo, were usually (65%–70%) associated with SLE flares across treatment groups, and were generally thought to be unrelated to study drug. The rate of grade 3/4 hemoglobin reductions occurring during the trials was lower with belimumab 10 mg/kg vs. placebo (1.6% vs. 4.9%), and 50%–60% of patients with serious anemia or grade 3/4 hemoglobin reductions had a medical history of anemia.

Infusion and hypersensitivity reactions

Of patients experiencing infusion reactions (including hypersensitivity), 14.7% were treated with placebo, and 16.8%, 23.4%, and 16.9% with belimumab 1, 4, and 10 mg/kg, respectively

Table 3 Adverse events

	Standard therapy +			
	Placebo ($n=675$), %	Belimumab 1 mg/kg ($n=673$), %	Belimumab 4 mg/kg[a] ($n=111$), %	Belimumab 10 mg/kg ($n=674$), %
Overview				
≥1 AE	92.7	93.3	96.4	93.0
≥1 serious AE[b]	16.6	19.5	13.5	18.0
≥1 severe AE[c]	15.9	15.9	23.4	15.4
≥1 serious and/or severe AE[b,c]	22.4	24.1	28.8	23.3
Death	0.4	0.7	0	0.9
Common AEs (occurring in ≥10% in any treatment group)				
Headache	20.7	21.2	27.0	21.5
Upper respiratory tract infection	20.4	19.3	32.4	17.7
Arthralgia	17.3	15.5	28.8	16.8
Nausea	12.6	13.4	19.8	15.1
Urinary tract infection	12.7	14.3	17.1	13.4
Diarrhea	9.9	12.2	20.7	12.2
Fatigue	10.5	10.5	29.7	9.8
Serious AEs (occurring in ≥1% in any treatment group)[b]				
Pneumonia	1.5	1.0	0.9	0.9
Urinary tract infection	0.7	1.0	0.9	0.7
Lupus nephritis	0.7	0.7	0	1.0
Pyrexia	0.4	0.7	0	1.3
Cellulitis	0.3	1.0	0.9	0.1
Infusion and hypersensitivity reactions[d]				
All infusion/hypersensitivity AEs	14.7	16.8	23.4	16.9
Serious[b]	0.4	0.9	0	0.9
Resulting in discontinuation	0.3	0.6	0.9	1.0
All hypersensitivity AEs	0.1	1.3	1.8	0.4
Serious[b]	0	0.3	0	0.3
Resulting in discontinuation	0	0.3	0.9	0.3
Infections				
≥1 infection	67.4	71.9	79.3	70.8
≥1 serious infection[b]	5.5	7.1	6.3	5.3
≥1 severe infection[c]	3.4	3.9	5.4	2.7
Infection resulting in discontinuation	1.2	0.7	0.9	0.6
Infection resulting in death	0.1	0.1	0	0.4
Infections of special interest				
Cellulitis	6.7	8.9	8.1	6.4
Sepsis	0.4	0.6	0.9	0.7
Fungal	3.4	3.1	3.6	2.5
Herpes virus	8.0	8.3	4.5	6.8
All respiratory	49.5	52.0	59.5	53.0
Upper respiratory	44.4	45.0	55.0	45.8
Lower respiratory	8.9	11.9	11.7	12.3
Pneumonia	2.7	3.3	1.8	2.4
Opportunistic	0	0	0	0.3[e]
Other AEs of special interest				
Malignant neoplasm[f]	0.3	0.7	0	0.4
Psychiatric disorder	12.4	16.0	22.5	15.9
Serious psychiatric disorder[b]	0.4	0.6	0	1.2
Depression	4.0	6.2	10.8	5.8
Serious depression[b]	0.1	0.4	0	0.4
Suicide	0	0.1	0	0.1
Insomnia	5.5	6.1	4.5	7.0
Anxiety	2.8	4.5	6.3	2.2
Laboratory abnormalities (grade 3/4 in >2% in any treatment group), %				
White blood cells (<1999 mm^3)	3.7	2.7	4.5	4.2
Lymphocytes (<500/mm^3)	26.2	27.9	21.6	27.0
Neutrophils (<999/mm^3)	5.5	5.1	9.0	5.2
Hemoglobin (<8.0 g/dL)	4.9	3.6	4.5	1.6

(continued)

Table 3 Adverse events (continued)

	Standard therapy +			
	Placebo ($n=675$), %	Belimumab 1 mg/kg ($n=673$), %	Belimumab 4 mg/kg[a] ($n=111$), %	Belimumab 10 mg/kg ($n=674$), %
Prothrombin time (>1.5 × ULN)	8.4	9.8	19.8	9.3
γ-glutamyl-transferase (>5 × ULN)	4.3	2.8	4.5	3.9
Protein/creatinine ratio (>2 mg/mg)	12.1	11.1	6.3	11.7
Proteinuria (>2-g loss/24 h)	3.0	1.6	0	2.8
Immunoglobulin shifts from high/normal to low, %				
IgG (<LLN [6.94 g/L])	2.9 ($n=665$)	5.4 ($n=662$)	4.6 ($n=108$)	6.6 ($n=665$)
IgG <400–250 mg/dL[g]	0.2	0.2	0	0.2
IgA (<LLN [0.81 g/L])	1.2 ($n=653$)	2.0 ($n=651$)	3.7 ($n=108$)	2.7 ($n=659$)
IgM (<LLN [0.48 g/L])	6.3 ($n=652$)	17.7 ($n=651$)	21.3 ($n=108$)	19.9 ($n=658$)

AE: adverse event; Ig: immunoglobulin; LLN: lower limit of normal; ULN: upper limit of normal.
[a]The belimumab 4-mg/kg dose was administered only in the phase 2 trial; therefore, the safety of this dose can only be evaluated within the context of that study (as reported by Wallace et al[13]).
[b]Serious refers to an AE that results in death, an immediate threat to life, inpatient hospitalization, prolongation of an existing hospitalization, persistent or significant disability/incapacity, or a congenital anomaly/birth defect, or that is medically important.
[c]Severe refers to a grade 3/4 AE.
[d]Infusion reactions (comprising >70 preferred terms in 13 organ system classes) occurring on the day of infusion that resolved within 7 days, or hypersensitivity reactions (comprising the preferred terms anaphylactic reaction and shock, angioedema, drug hypersensitivity, hypersensitivity, and tachyphylaxis) occurring on the day of infusion irrespective of resolution date.
[e]1 report of *Acinetobacter* bacterium and 1 of disseminated cytomegalovirus.
[f]Included 1 basal-cell carcinoma and 1 carcinoid tumor of the stomach with placebo; 1 squamous-cell carcinoma of skin, 1 breast cancer, 1 cervical carcinoma (stage 0), 1 ovarian cancer (diagnosed with advanced disease on day 21), and 1 thyroid neoplasm with belimumab 1 mg/kg; and 2 squamous-cell carcinoma of skin and 1 basal-cell carcinoma with 10 mg/kg.
[g]Grade 3 hypogammaglobulinemia, with no cases of grade 4 (<250 mg/dL).

(Table 3). Serious and/or severe infusion reactions occurred in 0.6% of patients with placebo, and 1.2%, 0%, and 1.2% with belimumab 1, 4, and 10 mg/kg, respectively. Most infusion reactions occurred during the first two infusions; the highest incidence occurred with the first infusion (4.1% with placebo, and 5.8% with belimumab 1 mg/kg, 5.4% with 4 mg/kg, and 7.3% with 10 mg/kg) and declined with each subsequent infusion, whereas the incidence of all infusion reactions after the second dose was similar across treatment groups (0.9%–1.0%). There was one serious infusion reaction that occurred after the second dose (in the belimumab 1-mg/kg group following the third dose). Infusion reactions were not dose related. In a patient treated with belimumab 1 mg/kg, a serious infusion reaction of headache, myalgia, and erythematous skin rash occurred 3 h after completing the second infusion, and the patient was not rechallenged. Most infusion reactions were mild to moderate in severity and were managed with routine care (e.g. antihistamines, antipyretics). The most common infusion reactions with placebo, and belimumab 1, 4, and 10 mg/kg, respectively, were headache (4.0%, 3.7%, 5.4%, and 3.6%), nausea (2.8%, 2.5%, 5.4%, and 3.3%), pruritus (0.4%, 0.4%, 1.8%, and 0.4%), and erythematous rash (0.1%, 0.1%, 0%, and 0.3%). Two reported hypersensitivity reactions that occurred beyond the day of infusion were considered related to belimumab treatment: one patient treated with 1 mg/kg experienced symptoms of nausea, fatigue, body pain, headache, leg weakness, and rash 7 days after the seventh infusion, which led to discontinuation. Another patient treated with belimumab 10 mg/kg reported angioedema 39 days after the eighth infusion and continued on study.

Serious and/or severe hypersensitivity reactions (i.e. anaphylaxis, angioedema, and drug hypersensitivity) were reported in four patients receiving belimumab (two each in the 1- and 10-mg/kg groups). All four reactions occurred during the 2-h administration of the first dose, and all of these patients discontinued belimumab. Three of these cases were managed successfully with antihistamines and/or corticosteroids. One of these patients was taken to the emergency department with anaphylaxis and angioedema, and was treated with chlorpheniramine, methylprednisolone, ondansetron, subcutaneous epinephrine, oxygen, and paracetamol; the anaphylactic reaction resolved on the day of onset, and the angioedema began improving

within 1 day and was considered resolved within 11 days. None of these patients had anti-belimumab antibodies. Another patient treated with belimumab 1 mg/kg experienced allergy-related edema of the lungs during the third infusion, which may represent a hypersensitivity reaction. Symptoms resolved within 5 h. This patient discontinued belimumab.

Infections

Infection was the most commonly reported AE. The most frequent infections were upper respiratory tract infections, urinary tract infections, nasopharyngitis, sinusitis, bronchitis, and influenza. Infection rates were similar across treatment groups (Table 3). Lower respiratory tract infections were more common with belimumab vs. placebo (11.7%–12.3% vs. 8.9%), although rates of pneumonia were similar (1.8%–3.3% vs. 2.7%).

The most frequently reported serious infections (i.e. occurring in $\geq$3 patients in any treatment group) were pneumonia, urinary tract infections, cellulitis, bronchitis, herpes zoster, and pyelonephritis. Incidence rates of serious infections/100 patient-years were comparable between placebo (5.35 [95% confidence interval (CI) 3.77–7.37]) and belimumab (6.00 [4.83–7.37]).). There was an increase in serious and/or severe infections in patients treated with immunosuppressives (including mycophenolate mofetil) and/or prednisone compared with patients not treated with those agents. Incidences of infections and serious and/or severe infections were, however, generally similar across all treatment groups with or without immunosuppressives (including mycophenolate mofetil) and/or prednisone.

Three opportunistic infections were reported in two patients treated with belimumab 10 mg/kg and one patient with 1 mg/kg. All three cases were considered serious. In the belimumab 10-mg/kg group, a disseminated cytomegalovirus infection developed on day 62 and resolved after 52 days, and an *Acinetobacter* bacteremia noted on day 15 resolved after 28 days. This patient continued on study. The patient treated with belimumab 1 mg/kg had a serious bacterial pneumonia (*Acinetobacter iwolfii*) on day 1 (which, therefore, was not considered related to belimumab). It resolved with antibiotic treatment and the patient continued on study.

Infection was reported as the cause of death in one patient treated with standard therapy alone and four treated with belimumab. Three of the four infection-related deaths with belimumab involved sepsis and one was related to infectious diarrhea. The infection-related mortality rates per 100 patient-years were 0.14 (95% CI 0.00–0.81; 692 patient-years) with placebo and 0.26 (95% CI 0.07–0.68; 1516 patient-years) with belimumab 1, 4, and 10 mg/kg.

Malignancies

Three cases of malignancy occurred with placebo (breast, gastric, and skin-basal cell), four with belimumab 1 mg/kg (one each of breast, cervical, ovarian, and skin-squamous cell), zero with 4 mg/kg, and three with 10 mg/kg (one skin-basal cell and two skin-squamous cell). There was a thyroid neoplasm reported in a patient treated with belimumab 1 mg/kg that was not specified as malignant or benign; malignancy is unlikely since it was considered non-serious, no anticancer therapy was initiated, and belimumab treatment was continued.

The malignancy rates per 100 patient-years (excluding non-melanoma skin cancer) were comparable between patients treated with placebo (692 patient-years; rate 0.29 [95% CI 0.04–1.04]) and belimumab 1, 4, and 10 mg/kg (1516 patient-years; rate 0.20 [0.04–0.58]).

Psychiatric adverse events

Psychiatric AEs were reported more frequently with belimumab treatment than with standard therapy alone, driven primarily by depression-related AEs, insomnia, and anxiety (Table 3). There was a similar approximate two-fold greater likelihood across all treatment groups of developing a psychiatric disorder during the study if the patient had a medical history of psychiatric disorder, depression, anxiety, or insomnia, but not with a central nervous system medical history (data not shown). Serious psychiatric and depression AEs were reported at higher frequencies with belimumab than with standard therapy alone. One completed suicide each was reported in the belimumab 1- and 10-mg/kg groups. It should be noted that the rates of selective serotonin reuptake inhibitor use at baseline were 11.9%, 14.3%, 27.9%, and 13.4% with placebo, and belimumab 1, 4, and 10 mg/kg, respectively; the corresponding rates of other antidepressant use were 8.3%, 7.7%, 12.6%, and 8.0%.

Laboratory abnormalities

The incidence rates of severe laboratory abnormalities were similar across treatment groups (Table 3). As expected, lymphopenia ($<$500 lymphocytes/mm^3)

was the most frequent severe laboratory abnormality. The rates of severe prolonged prothrombin time (>1.5 times the upper limit of normal) were similar across treatment groups within each study (8%, 10%, 20%, and 9% with placebo, and belimumab 1, 4, and 10 mg/kg, respectively) and may have been related to the intake of warfarin among these patients.

Immunoglobulins

Reductions in IgG, IgA, and IgM are expected pharmacologic effects of belimumab. Shifts in IgG and IgA to below the lower limit of normal were infrequent, although more common with belimumab (Table 3). For IgG, shifts to below the lower limit of normal occurred in 5%–7% of patients treated with belimumab vs. 3% with placebo; no patients in the belimumab 4-mg/kg group and one patient in each of the other treatment groups had a shift to grade 3 hypogammaglobulinemia. Shifts in IgM from high or normal at baseline to below the lower limit of normal occurred in a higher proportion of patients treated with belimumab (18%–21%) than with placebo (6%). Patients with immunoglobulin levels below the lower limit of normal did not have an increased rate of infection.

Mortality

Fourteen deaths were reported during the blinded, randomized portions of the phase 2 and 3 trials: three with placebo, five with belimumab 1 mg/kg, none with 4-mg/kg, and six with 10 mg/kg. Another death, due to respiratory arrest, was reported in the belimumab 1-mg/kg group 104 days after the patient discontinued treatment due to acute renal failure on day 112. This death was considered SLE related by the investigator. Of the three deaths in the placebo group, one was due to unknown cause, one to infection, and one to cardiovascular disease. Of the 11 deaths with belimumab treatment, four were due to infections, one to SLE, two to suicides, and one each to cardiac disorder, cerebrovascular disorder, malignancy, and unknown cause.

The mortality rates per 100 patient-years in the phase 2 and 3 SLE trials were 0.43 (95% CI 0.09–1.27; 692 patient-years) with placebo and 0.73 (95% CI 0.36–1.30; 1516 patient-years) with belimumab 1, 4, and 10 mg/kg.

Pregnancy

Table 4 reports outcomes of pregnancies in the phase 2 and 3 trials, and their continuation studies. Of six pregnancies occurring with placebo, three ended in fetal loss, and three were electively terminated. Of 54 pregnancies with belimumab, 21 resulted in live births and 13 ended in fetal loss; an additional 10 pregnancies were electively terminated, six were ongoing, and the outcomes in four were unknown. Two of the live births with belimumab had congenital abnormalities: one had a chromosomal abnormality present in the mother, and the other had Dandy Walker Syndrome (congenital brain malformation involving the cerebellum and 4th ventricle). Approximately half of the pregnancy group receiving placebo and one-third receiving belimumab tested positive for anticardiolipin antibodies, and had higher rates of fetal loss (66.7% vs. 50.0% with placebo and 53.8% vs. 29.6% with belimumab).

Table 4 Pregnancy

	Placebo ($n = 624$)[a]	All belimumab ($n = 1942$)[b]
Pregnancies with known outcomes/total pregnancies, *n*	6/6	44/54
Live birth, *n* (%)	0	21 (47.7)[c]
Elective termination, *n* (%)	3 (50.0)	10 (22.7)
Fetal loss, *n* (%)	3 (50.0)	13 (29.5)
Spontaneous abortion	2 (33.3)	12 (27.3)
Stillbirth	1 (16.7)	1 (2.3)
Anticardiolipin positive, *n* (%)	3 (50)	16 (29.6)
In patients with live birth	–	4 (19.0)
In patients with fetal loss	2 (66.7)	7 (53.8)

[a]Women only.
[b]As of December 31, 2010; includes phase 2/3 placebo-controlled periods of the phase 2 and 3 trials, and the respective continuation studies.
[c]1 infant with chromosomal translocation (present in mother) expired several days after birth.

Discussion

Belimumab was generally well tolerated when administered over 52 or 76 weeks in combination with a wide range of standard SLE therapies. Rates of patients experiencing any AE, AEs leading to study agent discontinuation, and serious or severe AEs were similar across treatment groups. Among AEs reported in ≥10% of patients in any treatment group, only nausea, diarrhea, and urinary tract infection occurred more often with belimumab than placebo; however, the differences were numerically small and not statistically significant.

The incidence rates of serious infusion and hypersensitivity reactions, including anaphylaxis, were numerically higher with belimumab than placebo (0.8% vs. 0.4%), and occurred usually during the first or second infusion. Few infusion or hypersensitivity reactions led to study agent discontinuation, and the incidence of these reactions decreased after the second infusion. Some patients (13%) received premedication that may have mitigated or masked infusion or hypersensitivity reactions; however, there is insufficient evidence to determine whether premedication diminished the frequency or severity of these reactions.

Infections, which are among the most common causes of morbidity and mortality in the general SLE population,[15] were the most frequently reported AEs, serious AEs, and causes of death in the belimumab clinical trials. The rates of serious infections were similar across treatment groups. Although there was a greater proportion of patients receiving belimumab with IgG or IgM levels below normal, there was no apparent increased risk of infections in patients with immunoglobulin levels below the lower limits of normal compared with patients with normal levels. Opportunistic infections were rare on belimumab therapy, but long-term follow-up in greater numbers of patients is needed for a definitive assessment.

Systemic lupus erythematosus is associated with an increased risk of malignancies, particularly non-Hodgkin's lymphoma, cervical cancer, lung cancer, bronchial carcinoma, and hepatobiliary cancer.[16,17] No hematologic malignancies were reported during the blinded, randomized, controlled portions of the three belimumab studies included in this analysis. No pattern of malignancies or increase in any particular tumor type was identified with belimumab treatment other than would be expected in a predominantly female SLE population. The malignancy rate per 100 patient-years with belimumab (0.20 [95% CI 0.04–0.58]) was lower than that from a study of an international SLE cohort, which observed 410 cancers in 9547 patients (76,948 patient-years) during an average follow-up of 8 years (0.53; 0.48–0.59).[16] Both the belimumab and historical malignancy figures excluded non-melanoma skin cancers. Long-term data (i.e. beyond 18 months) on the risk of malignancies with belimumab treatment will need to be accumulated before definitive conclusions can be drawn, since malignancies are unlikely to emerge during 12–18 months of treatment.

The rates of psychiatric AEs, including depression, were higher with belimumab than with standard therapy alone, as was the rate of serious depression. In comparison with the general population, the rates of psychiatric conditions, including depression and suicide, are known to be higher in SLE.[18,19] Systemic lupus erythematosus is known to be associated with an elevated incidence of suicide.[20,21] Two patients receiving belimumab committed suicide, one each in the 1- and 10-mg/kg dosing groups; one was described as having worsening depression, and the other had a history of depressed mood and psychotic disorder, although the latter patient was not known to be in a depressive state during the time of the suicide.

Systemic lupus erythematosus significantly increases mortality.[3,4] Although there were numerically more deaths in the belimumab groups than with standard therapy alone in the present analysis, the mortality rates per 100 patient-years, including long-term data, were similar with belimumab and placebo, and lower than the historically reported rate (76,948 patient-years; rate 1.63 [95% CI 1.54–1.72]) derived from observations in a large SLE cohort ($N = 9547$) between 1958 and 2001.[3] It should be noted, however, that the 95% confidence intervals of the mortality rates with belimumab in this analysis are wide and overlapping. The historical rate may be an overestimate of the current rate, given the improvement in SLE mortality rates in the modern era.[22] The most common cause of death with belimumab treatment was infection, followed by cardiovascular disease.

Systemic lupus erythematosus increases pregnancy morbidity.[23] Spontaneous abortion has been reported in 21% and 14.6% of pregnancies in two series.[24,25] Anticardiolipin antibodies and hypertension during pregnancy have been significantly associated with fetal loss, premature birth, and intra-uterine growth restriction. In the present analysis, the rate of anticardiolipin antibody positivity was substantially higher among women who experienced fetal loss than in those with live births (Table 4). Fetal loss occurred in a smaller

proportion of patients receiving belimumab vs. placebo (30% vs. 50%), but the sample size was small. The fetal loss rate in this limited population was similar to those noted in previous reports of pregnancies in patients with SLE.[26–28] In these phase 2 and 3 belimumab trials, patients were directed to use medically accepted methods of contraception and underwent pregnancy tests prior to receiving each dose; if pregnancy was detected, treatment was immediately discontinued. The small number of pregnancies in this analysis did not provide sufficient data to assess the impact of confounders such as SLE disease activity on pregnancy outcome.[25,27]

The populations enrolled in the phase 2 and 3 belimumab trials had the types of disease manifestations found in the general SLE population (i.e. mucocutaneous, musculoskeletal, and immunologic involvement in the majority of patients).[13,29] These patients, however, had higher (moderate–severe) disease activity (average SELENA-SLEDAI score 9.6) at baseline, despite receiving standard SLE therapy, than that in the general SLE population. These safety results are, therefore, applicable to the general SLE population with at least moderate disease activity, and without severe lupus nephritis and severe central nervous system lupus, which were both excluded from the studies.

A larger dataset and longer-term data will be needed before a definitive conclusion on the safety of treatment with belimumab can be made. Further studies will also be needed to determine the efficacy and safety of belimumab in patients with active lupus nephritis, as well as in patients receiving concomitant treatment with IV cyclophosphamide or other biologic agents.

In summary, the safety data obtained from the phase 2 and 3 belimumab studies support the conclusion that belimumab in combination with standard SLE therapy was generally well tolerated in a predominantly autoantibody-positive population of patients with active SLE. As with other biologic immune-modulating therapies, treated patients should continue to be monitored for hypersensitivity reactions, infections, and malignancies.

Acknowledgments

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

Funding

The studies were supported by GlaxoSmithKline, Uxbridge, Middlesex, UK, and Human Genome Sciences, Inc., Rockville, Maryland, USA.

Conflict of interest

Drs Wallace and Levy have received consulting and speaking fees from GlaxoSmithKline (GSK) and Human Genome Sciences, Inc. (HGS). Dr Navarra has received speaking fees and research support from GSK and HGS, and is a member of their advisory boards. Drs Petri and Cervera have received consulting fees from GSK and HGS, and are members of their advisory boards. Dr Furie has received consulting fees, and research and travel support from GSK and HGS. Dr van Vollenhoven has received consulting fees, honoraria, and research support from GSK and HGS. Drs Cooper, Zhong, and Freimuth are employed by and own stock in HGS. The other authors declare that they have no conflicts of interest.

References

1 Cancro MP, D'Cruz ADP, Khamashta MA, *et al*. The role of B lymphocyte stimulator (BLyS) in systemic lupus erythematosus. *J Clin Invest* 2009; 119: 1066–1073.
2 Rahman A, Isenberg DA. Systemic lupus erythematosus. *N Engl J Med* 2008; 358: 929–939.
3 Bernatsky S, Boivin J-F, Joseph L, *et al*. Mortality in systemic lupus erythematosus. *Arthritis Rheum* 2006; 54: 2250–2257.
4 Campbell Jr R, 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: 458–464.
5 Parikh-Patel A, White RH, Allen M, *et al*. Cancer risk in a cohort of patients with systemic lupus erythematosus (SLE) in California. *Cancer Causes Control* 2008; 19: 887–994.
6 Urowitz MB, Gladman D, Ibañez D, *et al*. Accumulation of coronary artery disease risk factors over three years: data from an international inception cohort. *Arthritis Rheum* 2008; 59: 176–180.
7 Thumboo J, Strand V. Health-related quality of life in patients with systemic lupus erythematosus: an update. *Ann Acad Med Singapore* 2007; 36: 115–122.
8 Lesley R, Xu Y, Kalled SL, *et al*. Reduced competitiveness of autoantigen-engaged B cells due to increased dependence on BAFF. *Immunity* 2004; 20: 441–453.
9 Thien M, Phan TG, Gardam S, *et al*. Excess BAFF rescues self-reactive B cells from peripheral deletion and allows them to enter forbidden follicular and marginal zone niches. *Immunity* 2004; 20: 785–798.
10 Petri M, Stohl W, Chatham W, *et al*. Association of plasma B lymphocyte stimulator levels and disease activity in systemic lupus erythematosus. *Arthritis Rheum* 2008; 58: 2453–2459.
11 Furie R, Petri M, Zamani O, *et al*. BLISS-76 Study Group. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. *Arthritis Rheum* 2011; 63: 3918–3930.

12 Navarra SV, Guzmán RM, Gallacher AE, *et al*. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. *Lancet* 2011; 377: 721–731.
13 Wallace DJ, Stohl W, Furie RA, *et al*. A phase II, randomized, double-blind, placebo-controlled, dose-ranging study of belimumab in patients with active systemic lupus erythematosus. *Arthritis Rheum* 2009; 61: 1168–1178.
14 Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997; 40: 1725.
15 Navarra SV, Leynes MS. Infections in systemic lupus erythematosus. *Lupus* 2010; 19: 1419–1424.
16 Bernatsky S, Boivin J-F, Joseph L, *et al*. An international cohort study of cancer in systemic lupus erythematosus. *Arthritis Rheum* 2005; 52: 1481–1490.
17 Kiss E, Kovacs L, Szodoray P. Malignancies in systemic lupus erythematosus. *Autoimmun Rev* 2010; 9: 195–199.
18 Bachen EA, Chesney MA, Criswell LA. Prevalence of mood and anxiety disorders in women with systemic lupus erythematosus. *Arthritis Care Res* 2009; 61: 822–829.
19 Hanly JG, Urowitz MB, Sanchez-Guerrero J. Neuropsychiatric events at the time of diagnosis of systemic lupus erythematosus. *Arthritis Rheum* 2007; 56: 265–273.
20 Harris EC, Barraclough BM. Suicide as an outcome for medical disorders. *Medicine* 1994; 73: 281–296.
21 US Department of Health and Human Services; Food and Drug Administration; Center for Drug Evaluation and Research. Guidance for industry: suicidality: prospective assessment of occurrence in clinical trials. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM225130.pdf (Sept 2010, accessed 19 Sept 2011).
22 Systemic lupus erythematosus (SLE or lupus). Centers for Disease Control and Prevention Web site. 2011. Available at: http://www.cdc.gov/arthritis/basics/lupus.htm10 (Updated 1 August 2011, accessed 15 March 2012).
23 Lockshin MD, Kim M, Laskin CA, *et al*. Prediction of adverse pregnancy outcome by the presence of lupus anticoagulant, but not anticardiolipin antibody, in patients with antiphospholipid antibodies. *Arthritis Rheum* 2012; 64: 2311–2318.
24 Cortes-Hernandez J, Ordi-Ros J, Paredes F, *et al*. Clinical predictors of fetal and maternal outcome in systemic lupus erythematosus: a prospective study of 103 pregnancies. *Rheumatology* 2002; 41: 643–650.
25 Molad Y, Borkowski T, Monselise A, *et al*. Maternal and fetal outcome of lupus pregnancy: a prospective study of 29 pregnancies. *Lupus* 2005; 14: 145–151.
26 Andrade R, Sanchez ML, Alarcón GS, *et al*. Adverse pregnancy outcomes in women with systemic lupus erythematosus from a multiethnic US cohort: LUMINA (LUI). *Clin Exp Rheumatol* 2008; 26: 268–274.
27 Clowse MEB, Magder LS, Witter F, *et al*. The impact of increased lupus activity on obstetric outcomes. *Arthritis Rheum* 2005; 52: 514–521.
28 Rahman P, Gladman DD, Urowitz MD. Clinical predictors of fetal outcome in systemic lupus erythematosus. *J Rheumatol* 1998; 25: 1526–1530.
29 Manzi S, Sánchez-Guerrero J, Merrill JT, *et al;* on behalf of the BLISS-52 and BLISS-76 Study Groups. Effects of belimumab, a B lymphocyte stimulator-specific inhibitor, on disease activity across multiple organ domains in patients with systemic lupus erythematosus: combined results from two phase III trials. *Ann Rheum Dis* 2012; 71: 1833–1838.