

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125370

SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date: March 9, 2011

From: Badrul A. Chowdhury, MD, PhD *Badrul A Chowdhury*
Director, Division of Pulmonary, Allergy, and Rheumatology
Products, CDER, FDA

Subject: Division Director Summary Review

BLA Number: 125370

Applicant Name: Human Genome Sciences

Date of Submission: June 9, 2010

PDUFA Goal Date: March 10, 2011 (original goal date was December 9, 2010)

Proprietary Name: Benlysta

Established Name: Belimumab

Dosage form: Single use 5 mL or 20 mL glass vial, supplied as lyophilized powder

Strength: 120 mg or 400 mg per vial

Proposed Indications: Systemic Lupus Erythematosus (SLE)

Action: Approval

1. Introduction

Human Genome Sciences (HGS) submitted this BLA on June 9, 2010, for use of belimumab lyophilized powder for intravenous infusion, at a dose of 10 mg/kg at 2-week intervals for the first 3 doses and at 4-week intervals thereafter. (b) (4)
 in adult patients with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy. The submitted data are adequate to support approval of the BLA. This summary review will provide an overview of the application, with a focus on the clinical efficacy and safety studies.

The original PDUFA date for this application was December 9, 2010. On November 23, 2010, HGS submitted new analyses of suicidality safety data using a method that was not used in the original BLA submission. At the same time HGS also submitted a Risk Evaluation Mitigation Strategy (REMS) that included a Medication Guide to inform patients of the potential risks associated with the use of belimumab. This submission was considered a major amendment and the PDUFA clock was extended to March 10, 2011.

2. Background

SLE is a prototypic autoimmune disease with diverse clinical manifestations in association with autoantibodies to components of the cell nucleus. SLE is primarily a disease of young women with a peak incidence between the ages of 15 and 40 years and a female:male ratio of 6-10:1. SLE prevalence estimates in the United States vary widely

with a reported range of as high as 1,500,000¹ to as low as 161,000 with definite SLE and 322,000 with definite or probable SLE.² The annual number of deaths with SLE as the underlying cause was reported as 879 to 1,406 from 1979 to 1998, with the highest number reported among black women 45-64 years of age.³ Patients with SLE have 80-90% survival at 10 years.⁴

The clinical presentation of SLE is diverse and includes a constellation of signs and symptoms involving various organs with an undulating course and accumulation of organ involvement over time. With rare exception, the unifying laboratory abnormality of SLE is the presence of circulating antinuclear antibodies. The American College of Rheumatology (ACR) has designated 11 classification criteria incorporating major clinical features (mucocutaneous, articular, serosal, renal, and neurologic) and laboratory findings (hematologic and immunologic) for diagnosis of SLE (Table 1).⁵ The presence of 4 or more criteria occurring either simultaneously or in succession is suggestive of the diagnosis of SLE.

Table 1. ACR 1997 revised classification criteria of SLE. The ACR requires 4 of these 11 criteria simultaneously or in succession to be classified as having SLE.

Criterion	Definition/Examples
1. Malar rash	Fixed erythema over the malar eminences, tending to spare nasolabial folds
2. Discoid rash	Erythematous raised patches, may scar
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight
4. Oral ulcers	Usually painless
5. Arthritis	Non-erosive, involving one or more peripheral joints
6. Serositis	a. Pleuritis, OR b. Pericarditis
7. Renal disorders	a. Persistent proteinuria (>3+ or 500 mcg/day), OR b. Cellular casts in urine
8. Neurological disorder	a. Seizures, OR b. Psychosis
9. Hematological disorder	a. Hemolytic anemia, OR b. Leukopenia (<4000/cmm total), OR c. Lymphopenia (<1500/cmm or two or more occasions), OR d. Thrombocytopenia (<100,000/cmm)
10. Immunological disorder	a. Anti-DNA antibody to native DNA in abnormal titer, OR b. Anti-SM antibody to SM nuclear antigen, OR c. Anti-phospholipid antibodies
11. Anti-nuclear antibody	Abnormal titer of ANA excluding drug causes

¹ Lawrence RC, Felson DT, Helmick CG, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States: Part II. *Arthritis Rheum* 2008; 58:26-35.

² Helmick CG, Felson DT, Lawrence RC, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States: Part I. *Arthritis Rheum* 2008; 58:15-25.

³ Sacks JJ, Helmick CG, Langmaid G, Sniezek JE. Trends in deaths from systemic lupus erythematosus – United States, 1979-1998. *MMWR* 2002; 51:371-374.

⁴ Boumpass DR, Fessler BJ, Austin HA, et al. Systemic lupus erythematosus: emerging concepts. *Ann Int Med* 1995; 123:42-53.

⁵ Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982; 25:1271-1277.

The more commonly involved organ systems are mucocutaneous, musculoskeletal, renal, nervous, cardiovascular, pleura, and lungs. The mucocutaneous and musculoskeletal systems are involved in over three-fourths of SLE patients. While these are debilitating and negatively impact the patients' quality of life, they are generally not fatal. Renal involvement occurs in one-half to two-thirds of patients and is associated with a poor outcome and mortality. Neuropsychiatric manifestations occur in about two-thirds of patients with varying manifestations, such as mood disorders, anxiety, and psychosis. Most patients with SLE also have general constitutional symptoms including fatigue, malaise, fever, anorexia, and weight loss. As mentioned above, the presence of anti-nuclear antibodies is the hallmark of the disease and is present in over 90% of patients.

The current standard of care for treatment of mild-to-moderate manifestations of SLE includes non-steroidal anti-inflammatory drugs (NSAIDs), antimalarial drugs such as hydroxychloroquine, and corticosteroids such as prednisone. Life-threatening manifestations of SLE, such as those involving the kidneys, central nervous system, or blood vessels are treated more aggressively with drugs such as high dose corticosteroids, or immunosuppressive agents such as cyclophosphamide and azathioprine, or both. Of these drugs, prednisone and hydroxychloroquine have FDA approved labeling for use in SLE. Currently there is no approved treatment for SLE that has been shown to prolong survival or reverse the course of the disease. SLE remains a disease with unmet medical need, especially for patients with active and life-threatening manifestations.

3. Chemistry, Manufacturing, and Controls

Belimumab drug substance is a human IgG1 λ monoclonal antibody that binds to soluble human B-lymphocyte stimulator (BLyS, also known as B cell activating factor or BAFF) and inhibits its biological activity. BLyS is a cytokine that belongs to the tumor necrosis factor (TNF) ligand family. It is expressed as transmembrane protein on various cell types including monocytes, dendritic cells, and bone marrow stromal cells. The transmembrane form can be cleaved from the membrane generating a soluble protein fragment. BLyS is a ligand for three receptors named BR3 (BLyS receptor 3), TACI (transmembrane activator-1 and calcium modulator and cyclophilin ligand-interactor), and BCMA (B-cell maturation antigen), which are all expressed on mature B-lymphocytes. TACI is also found on a subset of T-cells, and BCMA has been found on plasma cells. BLyS is the sole ligand for BR3, while BLyS and another member of the TNF ligand family called APRIL (A proliferation inducing ligand) are ligands for TACI and BCMA. The interaction between BLyS and BR3 is necessary for naïve B cells and mature primary B-cells, whereas the interaction between BLyS and either TACI or BCMA plays a role in the actions of antigen-activated B cells, memory B cells, and plasma cells. Therefore, the effect of belimumab is expected to be more on B cells early in ontogeny, such as naïve B cells, and less on B cells later in ontogeny, such as memory B cells and plasma cells because these cells will still receive signals through TACI and BCMA via APRIL.

The variable region of the belimumab molecule was derived from a phage display library made from a healthy human donor pool by screening for binding to recombinant BLyS.

The variable region was used to produce an expression vector construct to secrete full length IgG1 λ antibody in the NS0 mouse myeloma cell line using standard methodologies. Belimumab has a typical antibody structure with two identical heavy chains, two identical light chains, and a molecular weight of approximately 147 kDa. Belimumab drug product is a sterile lyophilized powder for reconstitution with sterile water for injection. Upon reconstitution with sterile water, each vial will contain 80 mg/mL belimumab in 0.16 mg/mL citric acid, 0.4 mg/mL polysorbate 80, 2.7 mg/mL sodium citrate, and 80 mg/mL sucrose, with a pH of 6.5. Each vial is for single use. There are 2 proposed configurations of belimumab: 120 mg in a 5 mL vial, and 400 mg in a 20 mL vial.

Belimumab drug substance will be manufactured at the (b) (4). The drug product will be manufactured at the (b) (4). All manufacturing and testing facilities associated with this application have acceptable inspection status. An expiry period of 36 months is proposed and supported by submitted data for belimumab drug substance and drug product.

There will be four CMC related post-marketing studies as described in section 13d.

4. Nonclinical Pharmacology and Toxicology

The nonclinical pharmacology and toxicology program for belimumab included general toxicity studies, and reproductive and developmental toxicity studies. The toxicology studies were performed using cynomolgus monkeys, which were deemed an appropriate species because belimumab was shown to bind to human and cynomolgus monkey with similar affinities. In the general toxicology studies, the findings of note were injection site reactions, lymphoid depletion in mesenteric lymph nodes, follicular degeneration of the thyroid, degeneration of kidney tubules and glomerular thickening, inflammation of the pancreas, peripheral B-cell depletion, and vasculitis. These findings had acceptable safety margins for human dosing or were considered to be monitorable in humans. In the reproductive and developmental toxicity studies there were fetal and infant deaths that occurred in all treatment groups including placebo and with no dose-related effect with belimumab. Belimumab was shown to cross the placenta and was excreted in milk in monkeys. Carcinogenicity studies were not conducted for belimumab for the following reasons: the lack of ability to complete standard 2-year bioassays in mice due to high anti-belimumab-antibody formation and death in some animals at repeated administration of belimumab; lack of increased rate of neoplasia observed in the A/WySNJ mouse that has a non-functional BR3/BAFF-R; and the absence of neoplasia in the chronic monkey study administered belimumab for 6-months with an 8-month recovery period.

5. Clinical Pharmacology and Biopharmaceutics

The pharmacokinetic (PK) assessment of belimumab was based on population PK analysis involving 1,512 females and 91 males diagnosed with SLE ranging in ages from 18 to 80 years from various clinical studies. Based on population estimates of the population PK model from the phase 3 studies, the systemic clearance was 215 mL/day,

the steady-state volume of distribution was 5.3 L, and the terminal half-life was 19.4 days for the belimumab 10 mg/kg dose. These results are consistent with results from other IgG1 monoclonal antibodies. Age, gender, and race did not significantly influence the belimumab pharmacokinetics. No formal studies were conducted to examine the effects of drug interaction, renal impairment, or hepatic impairment on the PK of belimumab. A thorough QT study was not done and is not expected because as a macromolecule belimumab would not be expected to affect the cardiac conduction system.

6. Clinical Microbiology

Not applicable.

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

Some characteristics of the relevant studies that form the basis of review and regulatory decision for this application are shown in Table 2. The main sources of efficacy and safety data are from studies L02, C1056, and C1057. Other studies are relatively small and of limited value and are not discussed further in this document. Design and conduct of these three studies are discussed below, followed by efficacy findings and safety findings.

Table 2. Relevant clinical studies

ID Year*	Study type	Study duration	Patient Age, yr	Treatment groups#	N (ITT)	Primary efficacy variables [†]	Countries [§] (% enrolled)
L01 2005	Phase 1 Safety	Single dose	20 - 65	Bel 1 mg/kg IV Bel 4 mg/kg IV Bel 10 mg/kg IV Bel 20 mg/kg IV Placebo	70	Not applicable	US (100%)
L02 2006	Phase 2 Efficacy and Safety	52 week	20 - 75	Bel 1 mg/kg IV Bel 4 mg/kg IV Bel 10 mg/kg IV Placebo	114 111 111 113	SELENA-SLEDAI SLE Flare Index	US (98%), Canada (2%)
C1056 2009	Phase 3 Efficacy and Safety	76 week	18 - 73	Bel 1 mg/kg IV Bel 10 mg/kg IV Placebo	271 273 275	SRI consisting of: SELENA-SLEDAI BILAG PGA	US and Canada (53%), W Europe (25%), E Europe (11%), LA (11%)
C1057 2009	Phase 3 Efficacy and Safety	48 week	18 - 71	Bel 1 mg/kg IV Bel 10 mg/kg IV Placebo	288 290 287	SRI consisting of: SELENA-SLEDAI BILAG PGA	LA (50%), Asia (38%), E Europe and Australia (13%)
L99 2006	Safety extension of L02	24 week		Bel 10 mg/kg IV	296	Not applicable	US and Canada (100%)
C1066	Safety extension of C1056	Ongoing		Bel 1 mg/kg IV Bel 10 mg/kg IV	85** 148**	Not applicable	
C1074	Safety extension of C1057	Ongoing		Bel 1 mg/kg IV Bel 10 mg/kg IV	235** 477**	Not applicable	

*Year study subject enrollment ended

** The N is through data cut-off date of December 31, 2009

ID Year*	Study type	Study duration	Patient Age, yr	Treatment groups#	N (ITT)	Primary efficacy variables [†]	Countries [§] (% enrolled)
# Bel = Belimumab 1, 4, or 10 mg/kg administration by IV infusion on days 0, 14, 28, and every 28 days thereafter							
[†] SRI = SLE Responder Index; SELENA-SLEDAI = Safety of estrogen in lupus erythematosus national assessment SLE disease Activity Index; BILAG = British Isles Lupus Activity Group; PGA = physician global assessment							
[§] W Europe = Western Europe; E Europe = Eastern Europe; LA = Latin America - Americas excluding US and Canada							

b. Design and conduct of the studies

The two disease activity instruments used in the clinical studies are described below followed by the design and conduct of the clinical studies. An understanding of these instruments will help interpret the results described in subsequent sections.

SELENA-SLEDAI (Safety of Estrogen in Lupus Erythematosus National Assessment-SLE Disease Activity Index): The SLEDAI is a list of 24 items, 16 are clinical items (seizures, psychosis, organic brain syndrome, visual disturbance, cranial nerve disorder, lupus headache, cerebrovascular accident, vasculitis, arthritis, myositis, new rash, alopecia, mucosal ulcers, pleurisy, pericarditis, and fever), and 8 are laboratory results (urinary casts, hematuria, proteinuria, pyuria, low complement levels, increased DNA binding, thrombocytopenia, and leukopenia). These are scored based on whether these manifestations were present or absent in the previous 10 days. Organ involvement is weighted; for example, musculoskeletal and renal activities are each multiplied by 4, whereas central nervous system activity is multiplied by 8. The weighted organ manifestations are then summed into a final score, which can range from 0 to 105. Scores greater than 20 are rare. A SLEDAI of 6 or more has been shown to be consistent with active disease requiring therapy.⁶ A clinically meaningful difference has been reported to be an improvement of 6 points or worsening of 8 points.⁷ The SLEDAI was modified in the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) trial; this modification, known as the SELENA-SLEDAI, added clarity to some of the definitions of activity in the individual items but did not change the basic scoring system.

BILAG (British Isles Lupus Activity Group): The BILAG is an organ-specific 86 question assessment based on the principle of the healthcare provider's intent to treat, which requires the assessor to score organ manifestations as improved (=1), same (=2), worse (=3), or new (=4) over the last month. Within each organ system, multiple manifestations and laboratory tests are combined into a single score for that organ, which is done by a specific computer software program. The resulting scores for each organ can be A through E, where A is very active disease, B is moderate activity, C is mild stable disease, D is resolved activity, and E indicates the organ was never involved. There are eight headings: general, mucocutaneous, neuropsychiatric, musculoskeletal, cardiorespiratory, vasculitis, renal, and hematologic.

⁶ Abrahamowicz M, Fortin PR, duBerger R, et al. The relationship between disease activity and expert physician's decision to start major treatment in active systemic lupus erythematosus: a decision aid for development of entry criteria for clinical trials. *J Rheumatol* 1998; 25:277-284.

⁷ ACR Ad Hoc Committee on SLE Response Criteria. The American College of Rheumatology Response Criteria for Systemic Lupus Erythematosus Clinical Trials. *Arthritis & Rheum* 2004; 50: 3418-3426.

The clinical studies of importance are studies L02, C1056, and C1057. Studies C1056 and C1057 were conducted under a Special Protocol Agreement (SPA) with the Agency.

L02 was a randomized, dose-ranging, placebo controlled study conducted in patients with a clinical diagnosis of SLE according to the ACR criteria. Patients were not required to be positive for autoantibodies. After meeting eligibility criteria, patients were randomized to placebo or 1, 4, or 10 mg/kg belimumab administration by IV infusion on days 0, 14, 28, and every 28 days thereafter for 48 weeks, over a background of standard SLE treatment. Background treatments allowed were the following (alone or in combination): prednisone from 5 to 40 mg/day when used alone or from 0 to 40 mg/day when used in combination with other SLE treatment, antimalarials, NSAIDs, or immunosuppressive therapy with methotrexate, azathioprine, leflunomide, or mycophenolate. Patients were required to be on stable background SLE treatment for a period of at least 30 days before randomization. Investigators could change a patients' background treatment as needed throughout the study. Primary efficacy endpoints were the percent change in SELENA-SLEDAI at week 24, and time to first SLE flare (as defined by the SELENA-SLEDAI flare index) over 52 weeks. Safety assessment included recording of adverse events, vital signs, clinical laboratory measures, physical examination, and development of antibodies to belimumab. Assessments of biomarkers, autoantibodies, and PK were also done.

C1056 and C1057 were also randomized, dose-ranging, placebo controlled studies conducted in patients with a clinical diagnosis of SLE according to the ACR criteria. Unlike study L02, patients in these two studies were required to be positive for autoantibodies (defined as ANA titer $\geq 1:80$ or anti-dsDNA level ≥ 30 I/mL at two points prior to randomization or both). Patients were also required to have currently active SLE (defined as SELENA-SLEDAI score ≥ 6 at screening), and were stratified by screening SELENA-SLEDAI score (6-9 vs ≥ 10). After meeting eligibility criteria, patients were randomized to placebo or 1 or 10 mg/kg belimumab administration by IV infusion on days 0, 14, 28, and every 28 days thereafter for 76 weeks (study C1056) or 48 weeks (study C1057), while on a background of standard SLE treatment. Background treatments allowed in these studies were similar to study L02 with the following notable differences: the dose of allowed prednisone was 7.5 to 40 mg/day when used alone; and allowable immunosuppressive therapies were expanded to include calcineurin inhibitors, sirolimus, oral cyclophosphamide, 6-mercaptopurine, and thalidomide. Unlike study L02, in these two studies comprehensive control on background treatments was implemented to help demonstrate efficacy of the investigational treatment. These two studies permitted no new immunosuppressive agents after randomization, no increase in immunosuppressive dose after week 16, no new antimalarials or increase in antimalarial dose after week 16, and greater control of increases in steroid dose after week 24. Patients requiring changes to background medication were declared treatment failures for efficacy assessment and were to have investigational treatment discontinued. Primary efficacy endpoints in these two studies were different than study L02. The primary efficacy endpoint was the proportion of responders at week 52 for a composite called the SLE Responder Index (SRI). SRI was defined as ≥ 4 point reduction in SELENA-SLEDAI score compared to baseline, and, no worsening (increase < 0.3 points from

baseline) in physician global assessment (PGA) score, and, no new BILAG A organ domain scores or 2 new BILAG B organ domain scores at time of assessment (i.e., week 52) compared to baseline. The SRI includes a measure of reduction in disease activity (SELENA-SLEDAI) and two measures to ensure that improvement in disease activity is not offset by deterioration in overall condition (PGA) or worsening in any specific organ system (BILAG). Safety assessment in the two studies included recording of adverse events, vital signs, clinical laboratory measures, physical examination, and development of antibodies to belimumab. Assessments of biomarkers, autoantibodies, and PK were also done.

c. Efficacy findings and conclusions

The clinical program showed that belimumab at the dose of 10 mg/kg reduced disease activity in adult patients with active, autoantibody-positive SLE who were receiving standard therapy. In subsequent sections efficacy data from the three studies of importance (Studies L02, C1056, and C1057) are presented with comments, followed by a summary.

Study L02 randomized a total of 449 patients of whom 364 completed the 52-week treatment period. The overall dropout rate was 19% (85 of 449) with no apparent difference among treatment groups. The baseline level of disease activity was high with a mean SELENA-SLEDAI score of 9.6. At baseline 72% of patients were positive for autoantibodies (ANA titer $\geq 1:80$ or anti-dsDNA level ≥ 30 I/mL or both). The co-primary efficacy endpoint, percent change in SELENA-SLEDAI at week 24, and time to first SLE flare (as defined by the SELENA-SLEDAI flare index) over 52 weeks were not met and did not show a dose response (Table 3). On post-hoc analysis, a trend toward efficacy was observed for all doses of belimumab in patients who were positive for autoantibodies, and had baseline prednisone dose >7.5 mg/day. The 10 mg/kg dose of belimumab appeared to have a faster onset of action and better potential for steroid sparing effect compared with lower doses. The SRI (composite endpoint used in the subsequent phase 3 studies) showed separation between placebo and all three active treatments in a subset of autoantibody positive patients. These findings guided the design and conduct of the two phase 3 studies (C1056 and C1057) where patients were required to be autoantibody positive, and comprehensive control of background treatment was implemented to enrich the patient population to help demonstrate efficacy of belimumab.

Table 3. Primary efficacy endpoint results for study L02

	Placebo (n=113)	Belimumab 1 mg/kg (n=114)	Belimumab 4 mg/kg (n=111)	Belimumab 10 mg/kg (n=111)
Percent change in SELENA-SLEDAI at week 24				
Mean difference from placebo		-6.10	5.94	-6.48
95% CI for mean difference		-19.4, 7.2	-8.7, 20.6	-19.6, 6.6
p-value		0.3677	0.4244	0.3296
Median time to first SLE flare over 52 weeks (days)				
Median time to first flare	83.0	68.0	61.0	70.0
p-value		0.6423	0.8536	0.9705
Total number of flares	329	320	307	329
Mean number of flares/subject	2.9	2.8	2.8	3.0

Studies C1056 and C1057 randomized a total of 1,684 patients. Study C1056 was conducted primarily in the US, Canada, and Western Europe (78% of patients were enrolled from these regions). Study C1057 was conducted primarily in Latin America and Asia (88% of patients were enrolled from these regions). The overall dropout rate in the studies at 52 weeks ranged from 17% to 26% with a slightly higher rate in placebo treatment arms compared to active treatment arms (difference ranged from 3% to 6%). The baseline level of disease activity was high with a mean SELENA-SLEDAI score of 9.67 for study C1056 and 9.75 for study C1057. The most commonly involved organ systems at baseline based on BILAG were musculoskeletal (60%), mucocutaneous (59%), hematologic (16%), renal (11%), general (11%), and vasculitis (9.0%). Patients between the two studies were comparable except for lower baseline disease activity in study C1056 compared to C1057, and lower baseline corticosteroid use in study C1056 (76% patients) compared to study C1057 (96% patients).

On the primary efficacy endpoint, belimumab 10 mg/kg was statistically significantly different from placebo in both the studies, and belimumab 1 mg/kg was statistically significantly different from placebo in one study (Table 4). Some post-hoc sensitivity analyses of the primary endpoint and secondary endpoints supported the primary endpoint, while some did not (data not shown in this document).

Table 4. Primary efficacy endpoint results for studies C1056 and C1057 at week 52

	Study C1056			Study C1057		
	Placebo (n=275)	Belimumab 1 mg/kg (n=271)	Belimumab 10 mg/kg (n=273)	Placebo (n=287)	Belimumab 1 mg/kg (n=288)	Belimumab 10 mg/kg (n=290)
Primary endpoint						
SRI (SLE Responder Index)	93 (34%)	110 (41%)	118 (43%)	125 (44%)	148 (51%)	167 (58%)
Difference vs pbo		7%	9%		8%	14%
OR (95% CI vs pbo)		1.34 (0.94, 1.91)	1.52 (1.07, 2.15)		1.55 (1.10, 2.19)	1.83 (1.3, 2.59)
p-value		0.1041	0.0207		0.0129	0.0006
Subcomponents						
4-point reduction in SELENA-SLEDAI	98 (36%)	116 (43%)	128 (47%)	132 (46%)	153 (53%)	169 (58%)
OR (95% CI vs pbo)		1.36 (0.96, 1.93)	1.63 (1.15, 2.32)		1.51 (1.07, 2.14)	1.71 (1.21, 2.41)
p-value		0.0869	0.0062		0.0189	0.0024
No worsening in PGA	173 (63%)	197 (73%)	189 (69%)	199 (69%)	227 (79%)	231 (80%)
OR (95% CI vs pbo)		1.60 (1.11, 2.30)	1.32 (0.92, 1.90)		1.68 (1.15, 2.47)	1.74 (1.18, 2.55)
p-value		0.0120	0.1258		0.0078	0.0048
No new BILAG	179 (65%)	203 (75%)	189 (69%)	210 (73%)	226 (79%)	236 (81%)
OR (95% CI vs pbo)		1.63 (1.12, 2.37)	1.20 (0.84, 1.73)		1.38 (0.93, 2.04)	1.62 (1.09, 2.42)
p-value		0.0108	0.3193		0.1064	0.0181

Various analyses of the data raise questions about the robustness of the efficacy findings of belimumab. These are discussed below.

First, the most commonly involved organ systems in the patients at baseline were musculoskeletal and mucocutaneous, which are debilitating in terms of impairing quality of life, but are not generally fatal. Improvement with belimumab shown in the clinical studies was largely due to the effects on these organ systems. The data are not adequate to demonstrate efficacy in organ involvement associated with poor outcome and mortality, such as kidneys, central nervous system, and blood vessels.

Second, post-hoc analysis of racial subgroups suggest that there may be reversal in the direction of treatment effect in patients of African American or African heritage compared to other races. The SRI for patients of African American or African heritage in study C1056 were 39% (15 out of 39), 30% (12 out of 40), and 33% (13 out of 39), for placebo, belimumab 1 mg/kg, and belimumab 10 mg/kg, respectively. The SRI for patients of African American or African heritage in study C1057 were 64% (7 out of 11), 38% (3 out of 8), and 46% (5 out of 11), for placebo, belimumab 1 mg/kg, and belimumab 10 mg/kg, respectively. This is of concern because patients of African American or African heritage are known to have more aggressive SLE, often leading to worse outcomes.

Third, the data demonstrate an inconsistent efficacy trend across different geographical regions of the world with numerically smaller separation of efficacy measures between placebo and belimumab for patients from US and Canada compared to other regions. The SRI for patients from US and Canada in study C1056 were 32% (46 out of 145), 38% (59 out of 155), and 35% (47 out of 136), for placebo, belimumab 1 mg/kg, and belimumab 10 mg/kg, respectively. In comparison, the SRI for patients from Latin America in study C1057 were 49% (71 out of 145), 59% (85 out of 143), and 61% (85 out of 140), for placebo, belimumab 1 mg/kg, and belimumab 10 mg/kg, respectively.

Fourth, analysis of response over time and duration of response for study C1056 showed gradual separation between belimumab 10 mg/kg and placebo over time, which reached statistical significance at week 52, but lost statistical significance at week 76. Similarly, in study C1057 there was gradual separation between belimumab 10 mg/kg and placebo that reached statistical significance at week 52. A potentially slower onset of benefit and a potential lack of durability need to be considered because belimumab will be administered as a chronic treatment for SLE.

Summary

The clinical program of belimumab evolved over time (Table 1), with later studies C1056 and C1057 informed by data from early study L02. Study L02 targeted a broad spectrum of SLE patients and failed to show substantial efficacy. The later studies C1056 and C1057 targeted patients who were positive for autoantibodies and demonstrated efficacy. The results for the belimumab 10 mg/kg group in these two studies were consistent in demonstrating a statistically significant increase in the proportion of patients achieving a response, defined as a 4-point reduction in the SELNA-SLEDAI, no worsening in the physician global assessment, and no new BILAG domain scores. However, a reversal in

the direction of treatment effect in patients of African American or African heritage compared to other races was observed. Post-hoc exploratory analyses of the effect of treatment on various organ system manifestations overall suggest a treatment benefit with belimumab. There are some inconsistencies of efficacy as noted above and the numbers of patients with particular organ system involvement were small, which makes it difficult to draw definitive conclusions. Some of these inconsistencies do not preclude approval. These will be studied post-marketing as described in section 13d.

8. Safety

a. Safety database

The safety assessment of belimumab is based on the three randomized, placebo-controlled studies (L02, C1056, and C1057) and their safety extensions (Table 1). A total of 2,578 patients participated in the belimumab program with 2,272 receiving treatment with belimumab. The safety database is adequate.

b. Safety findings and conclusion

The safety data do not raise safety concerns that would preclude approval of belimumab for treatment of SLE. The safety findings of note with belimumab are numerical increase in all cause death, infections, malignancy, and suicides and psychiatric adverse events. These safety issues are briefly described below, followed by a summary.

Death:

There were a total of 14 deaths across the placebo-controlled, double-blind treatment periods (studies L02, C1056, and C1057), with 3 (0.4%), 5 (0.7%), and 6 (0.9%) occurring in patients in the placebo, belimumab 1 mg/kg, and belimumab 10 mg/kg group, respectively. One additional death in a patient treated with belimumab 1 mg/kg occurred 15 weeks after patient withdrawal. The death rate per 100 patient-years was 0.79 and 0.43 for belimumab and placebo, respectively, with a rate ratio of 1.83 (95% CI 0.49, 10.08). Even if the single patient in the belimumab group who died 15 weeks post-study withdrawal was removed from the exposure-adjusted analysis, the death rate with belimumab remains higher than for the placebo group (i.e. 0.73 versus 0.43). Of the 14 deaths that occurred in the placebo-controlled double-blind treatment periods, 2 occurred in study L02, 3 in study C1056, and 9 in study C1057. There were 4 deaths related to infection (1 in placebo group, 1 in belimumab 1 mg/kg group, and 2 in belimumab 10 mg/kg group). In addition there were 2 deaths where infection may have contributed to the deaths (1 in belimumab 1 mg/kg group, and 1 in belimumab 10 mg/kg group). There were 2 suicides, both in patients treated with belimumab (1 in belimumab 1 mg/kg group, and 1 in belimumab 10 mg/kg group). There was 1 cancer-related death in a patient treated with belimumab 1 mg/kg. The largest number of deaths was from study C1057, which was conducted primarily in Latin America and Asia (88% patients were enrolled from these regions). The absolute number of death in the clinical program was not very large and the overall data are not conclusive to link belimumab to death with certainty.

Serious Adverse Events⁸:

Infection was the most frequent serious adverse event with 5.2%, 6.8%, and 5.2%, occurring in patients in the placebo, belimumab 1 mg/kg, and belimumab 10 mg/kg groups, respectively. Psychiatric and nervous system serious adverse events were numerically more common with belimumab than with placebo. Depression was the most frequent serious adverse event under the psychiatric disorder system organ classification with 0.1% (1 patient), 0.4% (3 patients), and 0.4% (3 patients), occurring in patients in the placebo, belimumab 1 mg/kg, and belimumab 10 mg/kg groups, respectively.

Infections:

Infections associated with belimumab treatment deserve special attention given that the mechanism of action of belimumab is to inhibit BLyS, which directly affects B cell function. In the clinical program infections occurred more often with belimumab treated patients compared to placebo treated patients. The most frequent infections in the clinical program were upper respiratory tract infection (URTI), urinary tract infection (UTI), nasopharyngitis, sinusitis, and bronchitis. Of these, nasopharyngitis and bronchitis occurred more commonly with belimumab treatment compared to placebo. There were 2 opportunistic infections, both in the belimumab 10 mg/kg group. These included a disseminated CMV infection on day 62, and an Acinetobacter bacteremia on day 15. There were 4 infection related deaths with a numerical imbalance that favored placebo treatment over belimumab treatment as discussed above. The causes of these deaths were sepsis (placebo group), cellulitis leading to sepsis (belimumab 1 mg/kg group), cutaneous infection leading to sepsis (belimumab 10 mg/kg group), and infectious diarrhea (belimumab 10 mg/kg group).

Malignancy:

Malignancies associated with belimumab treatment deserve special attention given that belimumab affects the immune function. There were 5 solid organ malignancies in the clinical program. These included a stomach carcinoid (placebo group, day 202), a breast cancer (belimumab 1 mg/kg, day 102), a cervical cancer (belimumab 1 mg/kg, day 439), an ovarian cancer (belimumab 1 mg/kg, day 21, patient died), and a thyroid neoplasm (belimumab 1 mg/kg, day 378). There were 4 non-melanoma skin cancers, 2 basal cell carcinomas, and 2 squamous cell carcinomas (1 in the placebo group, 3 in the belimumab 10 mg/kg group). There were no reported solid organ malignancies in the belimumab 10 mg/kg group, and there were no reported hematological malignancies.

⁸ Serious Adverse Drug Experience is defined in 21 CFR 312.32 as any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience (defined in the same regulation as any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred), inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

Suicides and psychiatric events:

There were two completed suicides across the double-blind placebo controlled studies, both in patients treated with belimumab (one each in study L02 and study C1057). In addition there was another completed suicide in a belimumab treated patient during the safety extension period of study L02 (study L99). There were four cases of suicide attempts or suicidal ideation, all in patients treated with belimumab (one each in placebo-controlled studies L02 and C1057, and two in the safety extension period of study L02 called study L99). Psychiatric and nervous system adverse reactions classified as serious adverse events were numerically more common in patients treated with belimumab than with placebo. Depression was the most frequent serious adverse event under the psychiatric disorder category with 0.1% (1 patient), 0.4% (3 patients), and 0.4% (3 patients), occurring in patients in the placebo, belimumab 1 mg/kg, and belimumab 10 mg/kg groups, respectively. Psychiatric events not classified as serious adverse events, specifically depression/depressed mood, were more frequent in patients treated with belimumab than with placebo. The frequencies of depression/depressed mood were 30 (4.4%), 43 (6.4%), 12 (10.8%), and 36 (5.3%) in placebo, belimumab 1 mg/kg, belimumab 4 mg/kg, and belimumab 10 mg/kg groups, respectively. Although there is no known biological mechanism for suicides and psychiatric events with belimumab at this time, and patients with SLE are known to have neuropsychiatric events and are at higher risk of suicide^{9,10}, nevertheless, there was a numerical imbalance that favored placebo over belimumab in these double-blind placebo-controlled studies. In the original BLA submission HGS did not formally assess the safety database for treatment-emergent suicidality (suicidal ideation and behavior, both nonfatal and fatal suicide attempts) using commonly accepted methodologies, such as C-CASA codes and definitions,^{11,12} but submitted such analyses later within the review period in November 2010. The new and formal analyses did not reveal any new findings or new patterns. To further evaluate the significance of the imbalance, a consultation was obtained from Agency psychiatrists. The consult view was that the finding was not convincing, but a definitive conclusion could not be made from the limited data. The numbers of events were not very large, and there were no dose-response or temporal clustering. In the setting of anticipated high background rate,¹⁰ the data were not definitive.

Anaphylaxis, and Infusion Reactions:

The frequency of hypersensitivity reactions (including anaphylaxis) and infusion reactions combined was reported as 17% and 15%, in belimumab and placebo treatment arms, respectively. The reason for the observed high frequency in placebo treated patients is not clear. There were 3 cases of anaphylaxis in patients treated with

⁹ Bachen EA, Chesney MA, Criswell LA. Prevalence of mood and anxiety disorder in women with systemic lupus erythematosus. *Arthritis and Rheum* 2009; 61:822-829.

¹⁰ Harris EC, Barraclough BM. Suicide as an outcome for medical disorders. *Medicine* 1994; 73:281-296.

¹¹ FDA Draft Guidance for Industry on Suicidality: Prospective Assessment of Occurrence in Clinical Trials. Available at www.fda.gov/Drugs/Guidance

¹² Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): Classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressant. *Am J Psychiatry* 2007; 164:1035-1043.

belimumab compared to none in patients treated with placebo, which results in a relatively low frequency of anaphylaxis of 0.2% with belimumab. Adverse events of hypersensitivity and anaphylaxis cannot be captured with certainty from the existing database because the events were not prospectively coded using acceptable diagnostic criteria for anaphylaxis¹³, inconsistent pre-treatment with antihistamine and corticosteroids were allowed at the discretion of the investigator, and overlapping or incorrect coding of anaphylaxis as infusion reactions. Even with these limitations, it does not appear that anaphylaxis and infusion reactions are large safety signals for belimumab.

Immunogenicity:

Patients enrolled in clinical trials were tested for anti-drug antibody using a screening electrochemiluminescence assay followed by an inhibition or a neutralization assay. The assays were qualified and validated, but were found to have a problem with a high limit of detection for anti-drug antibodies. In the presence of 40 mcg/mL of belimumab in the serum the limit of detection was 2 mcg/mL for anti-drug antibody, which is rather high for such assays. Noting these limitations, the percentages of patients who remained negative for anti-drug antibody throughout the trials were 98.0%, 86.9%, and 99.1%, for placebo, belimumab 1 mg/kg, and belimumab 10 mg/kg, respectively. The highest rate of anti-drug antibody levels being observed in the lower dose of belimumab group may be due to less immunosuppression at the lower dose or may be due to interference by higher concentrations of belimumab in the serum with the higher dose of belimumab. As a post-marketing study, HGS will be asked to improve their assay to test for anti-drug antibody.

Summary

The belimumab clinical program has identified safety concerns as noted above, but these do not rise to a level that would preclude approval. The safety findings will be noted in the product label with appropriate level of warning and in the required Medication Guide. Some of the safety findings will be further studied post-marketing as described in section 13d.

c. REMS/RiskMAP

HGS has submitted a Medication Guide only REMS to inform patients of the potential risk associated with the use of belimumab in SLE patients. The risk of death, infections, anaphylaxis, infusion reaction, and psychiatric adverse events including suicide will be addressed in the Medication Guide. Per the February 2011, Draft Guidance for Industry: Medication Guides – Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS), in most cases FDA expects to include a Medication Guide as part of a REMS only when the REMS includes elements to assure safe use. Thus, while a Medication Guide is required to communicate the potential risks of

¹³ Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: Summary report – Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006; 117:391-397.

belimumab to patients, a Medication Guide as part of a REMS is not necessary to ensure the benefits of belimumab outweigh the risks.

9. Advisory Committee Meeting

A meeting of the Arthritis Advisory Committee (AAC) meeting was held on November 16, 2010, to discuss this application. At the meeting efficacy and safety issues mentioned above in this review were discussed. Some members of the Committee had questions about the clinical relevance of the SRI endpoint, and expressed concerns about differing efficacy between study 1056 and study 1057, apparent lack of efficacy in patients of African American or African heritage, and apparent lack of efficacy for serious organ manifestations, such as kidneys and central nervous system. The Committee overall felt that there was adequate evidence to conclude that belimumab had a beneficial treatment effect, although it might be small or limited only to some manifestations of the disease, and patients not of African American or African heritage. Regarding safety, the Committee noted the imbalance in mortality, infections, malignancy, suicides, and psychiatric adverse events, but felt that the extent of these risks was acceptable. On voting questions, the committee voted favorably regarding whether there was substantial evidence of efficacy (10 yes, 5 no), and the safety profile of belimumab (14 yes, 1 no). Regarding the approvability question, which is essentially the sum of demonstration of efficacy and safety, the results were in favor of approval (13 yes, 2 no). The Committee recommended the labeling be clear about limitations of efficacy, and that additional studies be done post-marketing to further assess efficacy, specially efficacy in patients of African American or African heritage, patients with lupus nephritis, and assess safety.

10. Pediatric

HGS requested a waiver for studies in patients 0-5 years of age and below with justification that such studies would be impractical because SLE is very rare in this age group, and a deferral for studies in patients with SLE ages 5 to 17 years. The waiver and deferral proposal was discussed at the PeRC meeting held on October 6, 2010. The PeRC agreed with the proposal of deferral and waiver.

HGS has submitted a protocol outline for a (b) (4) study (b) (4) for patients 5 to 17 years of age (b) (4). This proposed study with some modification will become a PREA required pediatric study.

11. Other Relevant Regulatory Issues

a. DSI Audits

A DSI audit was requested for 3 clinical study sites based on high enrollment and favorable outcome for belimumab. Final reports of the DSI inspections revealed adherence to Good Clinical Practices. Minor deficiencies were noted, but these were isolated and deemed unlikely to impact data integrity and patient safety. During review of the submission no irregularities were found that would raise concerns regarding data

integrity. No ethical issues were present. All studies were performed in accordance with acceptable ethical standards.

b. Financial Disclosure

HGS submitted acceptable financial disclosure statements. HGS reported that none of the investigators involved with the clinical studies had a proprietary interest in the product or significant equity in HGS.

c. Others

There are no outstanding issues with consults received from DDMAC, DMEPA, or from other groups in CDER.

12. Labeling

a. Proprietary Name

The proposed proprietary name Benlysta was reviewed by DMEPA and DDMAC and found to be acceptable.

b. Physician Labeling

HGS submitted a label in the Physician's Labeling Rule format. The label was reviewed by various disciplines of this Division, DRISK, DMEPA, and by DDMAC. Various changes to different sections of the label were done to reflect the data accurately and better communicate the findings to health care providers. The label contains efficacy data from clinical trials L02, C1056, and C1057 (Table 1), including negative findings, to explain the limited indication in a specified SLE population that is supported by the submitted data. Safety findings of mortality imbalance, infections, suicides, and psychiatric adverse events are described in the Warnings and Precautions section as well as in a Medication Guide as mentioned above. The Division and HGS have agreed on the final labeling language.

c. Carton and Immediate Container Labels

The labels were reviewed by various disciplines of this Division, OBP, and DMEPA, and were found to be acceptable.

d. Patient Labeling and Medication Guide

A Medication Guide was required as discussed in section 8c above.

13. Action and Risk Benefit Assessment

a. Regulatory Action

The applicant has submitted adequate data to support approval of belimumab lyophilized powder for intravenous infusion, at a dose of 10 mg/kg at 2-week intervals for the first 3 doses and at 4-week intervals thereafter, ^{(b) (4)} in adult patients with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy. The recommended action for this application is Approval.

b. Risk Benefit Assessment

The overall risk benefit assessment supports approval of belimumab. The safety findings of note with belimumab are numerical increase in all cause death, infections, malignancy, and suicides and psychiatric adverse events. The extent of these risks are acceptable and do not rise to a level that would preclude approval. The safety findings are noted in the product label with appropriate level of warning and in the required Medication Guide. Efficacy findings from the latter two studies (C1056 and C1057) were consistent in demonstrating a statistically significant difference for the primary efficacy endpoint favoring belimumab over placebo. There was an apparent lack of efficacy in patients of African American or African heritage, and for serious organ manifestations, such as kidneys and central nervous system. Nevertheless, there was adequate evidence to conclude that belimumab had a beneficial treatment effect, although it might be small or limited to only to some manifestations of the disease. The limitations of efficacy are reflected in the product label.

c. Post-marketing Risk Management Activities

HGS has submitted a Medication Guide only REMS to inform patients of the potential risk associated with the use of belimumab in SLE patients. The risk of death, infections, anaphylaxis, infusion reaction, and psychiatric adverse events including suicide will be addressed in the Medication Guide. Per the February 2011, Draft Guidance for Industry: Medication Guides – Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS), in most cases FDA expects to include a Medication Guide as part of a REMS only when the REMS includes elements to assure safe use. Thus, while a Medication Guide is required to communicate the potential risks of belimumab to patients, a Medication Guide as part of a REMS is not necessary to ensure the benefits of belimumab outweigh the risks. A

d. Post-marketing Study Commitments

There will be various post-marketing required (PMR) studies and post-marketing commitment studies (PMC) to further characterize the safety and efficacy of belimumab.

The PMR clinical studies will be as follows:

1. Randomized, controlled clinical trial to evaluate safety issues of interest, such as mortality, infection, malignancy, suicides, and psychiatric adverse events. The applicant proposed a 5,000-patient, 5-year study

(b) (4)

(b) (4)

The sample size, and thus the relative risks that can be ruled out, may be limited by the infeasibility of conducting a larger study, given the limited patient population. Agreement on the final details of this PMR trial is pending future discussion and evaluation of the full protocol when submitted.

2. Pregnancy registry to assess the outcome of pregnancy in SLE patients being treated with belimumab. Such a study is necessary because SLE is common in female of childbearing potential.
3. PREA-required pediatric study in 100 patients 5 to 17 years of age.

4. A controlled vaccination trial to characterize the potential of belimumab impairing vaccination response. Such a study is necessary because belimumab targets B-cells.

The PMR CMC study will be as follows:

1. Development of improved immunogenicity assay to better characterize the formation of anti-drug antibody.

The PMC clinical studies will be as follows:

1. An efficacy and safety study in patients with lupus nephritis.
2. An efficacy and safety study in patients of African American or African heritage with SLE.
3. Submission of long-term extension study LBSL99.
4. Submission of long-term extension study C1066.
5. Submission of long-term extension study C1074.

The PMC CMC studies will be as follows:

1. Study to generate data to support microbial control over the [REDACTED] (b) (4) lifetime use.
2. Study to qualify the cap and validate the integrity of drug product container closure.
3. Study to provide quantitative data to demonstrate [REDACTED] (b) (4) [REDACTED]