FDA Briefing Package

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V. Draft Guidance for Industry: Suicidality – Prospective Assessment of Occurrence in Clinical Trials

VI. References

1. American College of Rheumatology Ad Hoc Committee on Systemic Lupus Erythematosus Response Criteria. Arthritis & Rheumatism 2004; 50 (11): 3418-3426.

2. Furie RA, Petri MA, et al. Novel Evidence-Based Systemic Lupus Erythematosus Responder Index. Arthritis & Rheumatism 2009; 61 (9): 1143-1151.

3. Gladman D, Ginzler E, et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for Systemic Lupus Erythematosus. Arthritis & Rheumatism 1996; 39(3): 363-369.

4. Gladman D, Ibanez D, Urowitz M. Systemic Lupus Erythematosus Disease Activity Index 200. J Rheumatol 2002; 29: 288-91.

5. Hay EM, Bacon PA, et al. The BILAG index: a reliable and valid instrument for measuring clinical disease activity in systemic lupus erythematosus. Quarterly Jour of Med 1993; 86: 447-458.

6. Petri M. Disease activity assessment in SLE: Do we have the right instruments? Ann Rheum Dis 2007; 66: iii61-iii64.

7. Petri M, Buyon J, Kim M. Classification and definition of major flares in SLE clinical trials. Lupus 1999; 8: 685-691.

Disclaimer Statement

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the Biologic Licensing Application for belimumab for reducing disease activity in adult patients with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

DIVISION DIRECTOR MEMORANDUM

Date: October 19, 2010

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

To: Members, Arthritis Advisory Committee

Subject: Overview of the FDA background materials for BLA# 125370, Benlysta (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, for reducing disease activity in adult patients with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy

Introduction

Thank you for your participation in the Arthritis Advisory Committee (AAC) meeting to be held on November 16, 2010. As members of the AAC you provide important expert scientific advice and recommendations to the US Food and Drug Administration (the Agency) on the regulatory decision making process related to the approval of a drug or biologic product for marketing in the United States. The upcoming meeting is to discuss the Biologic Licensing Application (BLA) from Human Genome Sciences, seeking approval for 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, for reducing disease activity in adult patients with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy. The proposed trade name for the product is Benlysta.

This memorandum summarizes the content of the Agency background material and the key issues and questions for discussion at the meeting. The materials prepared by the Agency contain findings and opinions based on reviews of information submitted by Human Genome Sciences. These background materials represent preliminary findings, and do not represent the final position of the Agency. An important piece in our decision on this application will be the opinions and input that we receive from you at this AAC meeting.

The materials to be discussed at this AAC meeting and the opinions we are seeking are primarily related to the clinical and statistical issues of the belimumab study results. Keep in mind that in the regulatory decision making process to determine approvability of a product, the Agency takes into consideration various other factors in addition to clinical and statistical issues, including manufacturing and controls of a product and preclinical considerations. These will not be the focus of this AAC meeting.

Attached are the background materials for this meeting. The background materials include the following: an FDA briefing document; FDA Guidance documents on Systemic Lupus Erythematosus, Lupus Nephritis Caused by Systemic Lupus Erythematosus, and Suicidality: Prospective Assessment of Occurrence in Clinical Trials; and some relevant publications.

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 1,500,000[1] 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. 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, these 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.

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[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.

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

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.

Product Information

Belimumab drug substance is a fully human IgG1λ 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 produce full length IgG1λ antibody in Chinese Hamster Ovary 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.

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.

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 renal impairment and hepatic impairment on the PK of belimumab.

Clinical and Statistical

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

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
# 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

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.

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,

[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.

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 ≥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.

Efficacy Findings

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 ≥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, baseline prednisone use was limited to 7.5 mg and above, 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 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 that warrant discussion at the AAC meeting. 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 some 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 is proposed to be administered as a chronic treatment for SLE.

Fifth, and finally, patients requiring certain protocol-specified background SLE medication changes were imputed as study treatment failures for the primary efficacy analysis and had study treatment discontinued. Subjects receiving protocol-prohibited or restricted background SLE medications (referred to by the sponsor as medication failures) occurred more in placebo treatment arm, which may have exaggerated the difference between placebo and belimumab for the primary endpoint analysis. Medication failures were more common overall in study C1056 than C1057; therefore, this imputation had more impact on the primary efficacy analysis in that study.

Safety findings

The safety database for belimumab is based primarily on the three randomized, placebo-controlled studies (L02, C1056, and C1057) and their safety extensions (Table 1). The discussion in this overview is focused primarily on the placebo-controlled portion of the studies and how the safety findings with belimumab compared with placebo. The primary safety population from these placebo-controlled studies comprises 2,133 patients with SLE. The safety findings are discussed below under different headings of interest that warrant further discussion at the AAC meeting.

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).

Serious Adverse Events[8]:

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 the 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

[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.

(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 cancer (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 1 mg/kg group). There were no reported solid organ malignancies in the belimumab 10 mg/kg group, and there were no reported hematological malignancies.

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 mechanisms 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. The applicant has not formally assessed 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]

[9] Bachen EA, Chesney MA, Criswell LA. Prevalence of mood and anxiety disorder in women with systemic lupus erythmatosus. 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

Immunogenicity, Anaphylaxis, and Infusion Reactions:

The rate of immunogenicity with belimumab was approximately 5% of patients in the randomized placebo-controlled studies. 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 belimumab compared to none in patients treated with placebo, which results in a relatively low frequency of anaphylaxis of 0.2% with belimumab. Further analysis of the entire safety database is necessary to determine the frequency of anaphylaxis and infusion reaction using accepted diagnostic criteria for anaphylaxis[13], accounting for patients who may have received incorrect treatment (belimumab instead of placebo), and also addressing the impact of pre-treatment with antihistamine and corticosteroids, which were allowed at the discretion of the investigator.

Benefit risk assessment

Replicate findings of statistically significant differences between belimumab 10 mg/kg and placebo were shown in SLE patients positive for autoantibodies; however, the robustness and the clinical meaning of the efficacy findings warrant discussion. The reasons, as discussed above under the efficacy findings, include efficacy largely due to improvement in musculoskeletal and mucocutaneous organ systems and not in organ systems associated with poor outcome and mortality; lack of demonstrated efficacy in patients of African American or African heritage; inconsistent efficacy trend across different geographical regions of the world; seemingly slow onset of response and lack of durability of the response; and sensitivity analyses altering the approach to classifying patients as treatment failures because of requiring background SLE medication change show marginal efficacy results. The risks associated with belimumab include infection, malignancy, suicidality, and overall number of deaths with a numerical imbalance that favored placebo treatment over belimumab treatment. We are asking for discussion and your opinions at this AAC meeting on whether the degree of efficacy demonstrated in these trials is worth the risks of treatment with belimumab in SLE patients positive for autoantibodies. We are also asking for discussion on whether the potential benefits of belimumab outweigh the anticipated risk of treatment with belimumab if combined with other immunosuppressive agents, which may be needed to treat more serious SLE manifestations that are associated with poor outcome and mortality.

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[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.

[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.

Summary

The purpose of the AAC meeting is to discuss the adequacy of the efficacy and safety data submitted by Human Genome Sciences to support the approval of belimumab for reducing disease activity in adult patients with active autoantibody-positive SLE who are receiving standard therapy. This is an important discussion as belimumab is a new molecular entity and targets a novel pathway to potentially treat SLE.

At the AAC meeting, Human Genome Sciences will present an overview of the clinical program and efficacy and safety data, which will be followed by the Agency's presentation of the efficacy and safety data. Please keep in mind the following questions that will be discussed and deliberated upon following the presentations and discussion. Some of the questions are for discussion only, and some are for discussion and voting.

Draft Questions

1. Discuss the efficacy data of belimumab considering the following
    a) Efficacy driven by contribution of musculoskeletal and mucocutaneous organ systems results
    b) Lack of efficacy in organ systems associated with poor outcome and mortality in systemic lupus erythematosus
    c) Lack of demonstrated efficacy in patients of African American or African heritage
    d) Numerically smaller efficacy results for patients from US and Canada compared to some other regions

2. Discuss the overall safety profile of belimumab considering the following
    a) Safety signals of infection, malignancy, suicidality, and mortality imbalance favoring placebo over belimumab
    b) Potential risk of using belimumab when combined with other immunosuppressive agents, which may be needed to treat more serious manifestations of systemic lupus erythematosus that are associated with poor outcome and mortality

3. Discuss the suicidality data and provide recommendations for further evaluation, if necessary

4. Considering the totality of the data, has belimumab at a dose of 10 mg/kg at 2-week intervals for the first 3 doses and at 4-week intervals thereafter demonstrated substantial evidence of efficacy for reducing disease activity in adult patients with active, autoantibody-positive, systemic lupus erythematosus who are receiving standard therapy? **(Voting Question)**

    a) If not, what further efficacy data should be obtained?

5. Is the safety profile of belimumab sufficient for approval for reducing disease activity in adult patients with active, autoantibody-positive, systemic lupus erythematosus who are receiving standard therapy? **(Voting Question)**

    a) If not, what further safety data should be obtained?

6. Do the efficacy and safety data provide substantial evidence to support approval of belimumab at a dose of 10 mg/kg at 2-week interval for the first 3 doses and at 4-week intervals thereafter demonstrated substantial evidence of efficacy for reducing disease activity in adult patients with active, autoantibody-positive, systemic lupus erythematosus who are receiving standard therapy? **(Voting question)**

Briefing Document for the Arthritis Advisory Committee Meeting

November 16, 2010

Benlysta®/Belimumab
BLA 125370

Department of Health & Human Services

Food & Drug Administration
Center for Drug Evaluation & Research
Division of Pulmonary, Allergy and Rheumatology Products
Silver Spring, MD 20993

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Summary of FDA Review of Clinical Efficacy & Safety

Background

Background on Systemic Lupus Erythematosus

Systemic Lupus Erythematosus (SLE) is a heterogeneous autoimmune disease with clinical manifestations that can range from mild to life-threatening, affecting a variety of organ systems. Estimated incidence rates of SLE range from 1 to 10 per 100,000 person-years, with a prevalence in the range of 20 to 70 per 100,000. There is a consistent and striking female predominance, with females comprising approximately 90% of all SLE patients.[1] In general, the most common SLE manifestations are malar rash, photosensitivity, oral ulcers, arthritis, and renal disease. The incidence and severity of specific SLE manifestations appears to vary by ethnicity—compared to SLE patients of European descent, patients of African descent develop renal disease more frequently (~50%, vs. 20 to30% in patients of European descent) and the disease is more severe. High rates (60 to70%) of renal involvement are also reported in most Asian populations. Other less common but serious manifestations include serositis (16 to 64%, depending on population and report), neurological disorders (9 to 36%), and immune-mediated cytopenias (4 to 43%).[2]

Table 1: ACR 1997 Revised Classification Criteria of SLE

1997 Update of the 1982 American College of Rheumatology Revised Criteria for Classification of Systemic Lupus Erythematosus (SLE)	
Criterion	**Definition**
1. Malar Rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid Rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral Ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Nonerosive Arthritis	Involving 2 or more peripheral joints, characterized by tenderness, swelling or effusion
6. Pleuritis or pericarditis	1. Pleuritis--convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion OR 2. Pericarditis--documented by electrocardiogram or rub or evidence of pericardial effusion
7. Renal Disorder	1. Persistent proteinuria >0.5 grams per day or > than 3+ if quantitation not performed, OR 2. Cellular casts--may be red cell, hemoglobin, granular, tubular, or mixed
8. Neurological Disorder	1. Seizures--in the absence of offending drugs or known metabolic derangements, e.g. uremia, ketoacidosis, or electrolyte imbalance, OR 2. Psychosis--in the absence of offending drugs or known metabolic derangements, e.g. uremia, ketoacidosis, or electrolyte imbalance
9. Hematologic Disorder	1. Hemolytic anemia--with reticulocytosis, OR 2. Leukopenia--<4000/mm^3 on at least 2 occasions, OR 3. Lymphopenia--<1500/mm^3 on at least 2 occasions, OR 4. Thrombocytopenia--<100,000/mm^3 in the absence of offending drugs
10. Immunologic Disorder	1. Anti-DNA: antibody to native NDA in abnormal titer, OR 2. Anti-Sm: presence of antibody to Sm nuclear antigen, OR 3. Positive finding of antiphospholipid antibodies: 1. abnormal serum level of IgG or IgM anticardiolipin antibodies 2. a positive test result for lupus anticoagulant using a standard method, or 3. a false-positive test result for at least 6 months confirmed by treponema pallidum immobilization or fluorescent treponemal antibody absorption test
11. Positive Antinuclear Antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs.

For the purpose of identifying patients in clinical studies, a person shall be said to have SLE if any 4 or more of these 11 criteria are present, serially or simultaneously, during any interval of observation.

[1] Pons-Estel et al. Semin Arthritis Rheum 2010 Feb ; 39:257-268
[2] Borchers et al. Autoimmunity Reviews 9 (2010):A277-A287

For the purposes of clinical trials, the ACR has established classification criteria to assist in uniformly identifying patients with SLE, as shown in Table 1, above. Generally patients are considered to have SLE if they meet at least 4 of the 11 mentioned criteria. These criteria indicate a minimal requirement, reflecting the heterogeneity of possible clinical manifestations with which an SLE patient may present, and do not ensure a definitive diagnosis of SLE.

SLE Disease Activity Outcome Measures

The heterogeneity in clinical manifestations and disease severity of SLE has made it necessary to utilize extensive and somewhat complicated disease activity measurement instruments, each of which has strengths and weaknesses. In the interest of limiting the information to what is germane for the application under discussion, only the British Isles Lupus Activity Group (BILAG) index and the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) will be discussed here:

1. BILAG—This 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 (as applicable) 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, requiring treatment with immunosuppressive therapy and/or prednisolone (or equivalent) dose of greater than 20 mg/day, B is moderate activity which would require a lower level of immunosuppressive therapy, C is mild stable disease, D is resolved activity, and E indicates the organ was never involved. Eight headings are included: general, mucocutaneous, neuropsychiatric, musculoskeletal, cardiorespiratory, vasculitis, renal, and hematologic.
2. SLEDAI—This is a list of 24 items, each with a definition of activity; 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 based on laboratory results (urinary casts, hematuria, proteinuria, pyuria, low complements, increased DNA binding, thrombocytopenia, and leukopenia). The assessor scores according to whether that organ manifestation was present or absent in the last 10 days. Organ involvement is weighted; for example arthritis and renal activity 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 ranges from 0 to 105. A SLEDAI of 6 or more has been shown to be consistent with active disease requiring therapy.[3] A clinically meaningful difference has been reported to be improvement of 6 points or worsening of 8 points.[4] The SLEDAI was modified in the Safety of Estrogens

[3] Abrahamowicz et al. J Rheumatol 1998; 25(2):277-284
[4] ACR Ad Hoc Committee on SLE Response Criteria, Arthritis & Rheum, November 2004, 50(11):3418-3426

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. The SELENA-SLEDAI was the index used in the belimumab pivotal trials.

There is obvious overlap between these disease activity indices. Some important differences include:

- Organ scores are not weighted by importance with the BILAG. Therefore the index does not make a distinction between worsening or improvement in serious vs. non-serious manifestations.
- SLEDAI scoring does take into account seriousness of the manifestation, however the concepts of "worsening" or "improvement" are not readily captured by the SLEDAI because of the dichotomous nature of the assessment (is the defined disease activity present or absent?)
- The BILAG incorporates "intention to treat" aspects and thus correlates somewhat better with Physician Global Assessment of disease activity.

The SLE Responder Index (SRI) used in Studies 1056 and 1057 is novel endpoint created based on exploratory analyses of LBSL02, with the intention of capturing clinically meaningful change, yet ensuring there would not be significant worsening in overall disease activity.[5] Using this composite index, a patient is defined as a responder if they have the following:

- ≥4-point reduction in the SELENA-SLEDAI score compared to baseline, AND
- No worsening (i.e. increase <0.3 points from baseline) in physician global assessment (PGA) 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.

Although minimal clinically important differences have been defined for the SELENA SLEDAI and PGA, and the BILAG was created on the principle of clinically important differences, it is not known what difference in the responder rate of the SRI would represent a clinically important difference between treatments. Of note, this endpoint was not otherwise validated prior to use in Studies 1056 and 1057, but was agreed upon by the Agency in a Special Protocol Assessment agreement.

Status of Drug Development in SLE

In stark contrast to the extensive effort and study that has gone into the many disease activity indices developed for use in SLE, there have been few products approved for SLE—corticosteroids, hydroxychloroquine, and aspirin. A number of promising treatments have been studied but none have succeeded in showing consistent and convincing efficacy. Whether this has been due to the treatments, the heterogeneity of the disease, the outcome measures, or a combination cannot be ascertained. However, it

[5] Furie et al., Arthritis & Rheum, 2009, 61(9):1143-1151

is clear that demonstrating efficacy of a product in SLE clinical trials has been a difficult task.

In light of this difficulty, the fact that Benlysta (belimumab) appears to have demonstrated efficacy for the primary endpoint in two controlled trials is notable. However whether Benlysta has convincingly demonstrated efficacy, and whether it provides a useful option in the therapeutic armamentarium for SLE remain open questions—questions for which the Agency is seeking the Committee's input.

Summary of Product Information

The Molecule and Mechanism of Action

Belimumab is a human IgG1, lambda first-in class therapeutic monoclonal antibody specific for B lymphocyte stimulator (BLyS; BAFF) that binds to soluble BLyS with high affinity. Belimumab was derived from a phage display library generated by amplification of the VH, Vkappa and Vlambda transcripts from B cells pooled from 43 healthy donors and screened for binding to recombinant BLyS. The selected clone was reversed engineered to produce the full length IgG1 heavy chain and full length lambda light chain.

BLyS is a member of the TNF ligand family that plays a role in B cell selection and survival and is expressed by many cells of the immune system. It is expressed as a cell surface trimer, which is cleaved by furin and released into circulation. There are three BLyS family receptors, BLyS receptor 3 (BR3), transmembrane activator-1 and calcium modulator and cyclophilin ligand-interactor (TACI) and B cell maturation antigen (BCMA) displaying different levels of expression and patterns through B cell development and across B cell subsets. BLyS is the sole ligand for BR3 while both TACI and BCMA bind to BLyS and another member of the TNF ligand family, a proliferation-inducing ligand (APRIL). The interaction between BLyS and BR3 is necessary for newly formed 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 long-lived plasma cells.

The belimumab mechanism of action (MOA) is through blocking BLyS binding to its three receptors. Thus, it would have more activity directed towards blockade of the survival of naïve B cells while memory B cells and plasma cells may still receive signals through TACI and BCMA via APRIL.

Belimumab has a typical antibody structure, composed of two identical H chains and two identical L chains, with a molecular weight of ~147 kDa. There is a typical heterogeneity at the H-chain N-terminus due to cyclization of glutamine to pyroglutamic acid and at the C-terminus of the H chain due to incomplete cleavage of the C-terminal lysine. This leads to a heterogeneous charge profile which does not impact the activity of belimumab.

Belimumab also contains a typical heterogeneous N-linked glycosylation profile in the CH2 domain of the H chain.

The potency assay for belimumab is designed to demonstrate belimumab inhibition of BLyS binding to a B cell line expressing all three BLyS receptors. In addition, belimumab has been shown to inhibit the proliferation of murine splenocytes and primary human B cells cultured with BLyS. Belimumab does not recognize the membrane-bound form of BLyS. Finally, belimumab glycosylation has been demonstrated to have no impact on binding to BLyS, suggesting that the MOA of belimumab does not involve its glycosylation.

Belimumab is expressed in a Chinese Hamster Ovary cell line and manufactured using typical bioreactor and purification methods for therapeutic monoclonal antibodies. Belimumab drug product is presented as a lyophilized product in two vial configurations to deliver belimumab at 80mg/mL after reconstitution with Water for Injection: a 400 mg/vial with a 5 mL deliverable volume and a 120mg/vial with a 1.5 mL deliverable volume.

The Pharmacology/Toxicology Program

Nonclinical safety evaluations include general toxicity, reproductive and developmental toxicity and carcinogenicity studies. The belimumab application has completed adequate general toxicity and reproductive toxicity studies in cynomolgus monkeys. The sponsor has not evaluated belimumab's carcinogenic potential.

Belimumab was shown to bind to both human and cynomolgus monkey BLyS protein with similar affinity and activity demonstrating that the cynomolgus monkey was an appropriate species in which to characterize its pharmacological and toxicological profile. Belimumab neutralizes BLyS which results in a reduction of B cell numbers. In the repeat dose toxicity study, the drug product reduced the B-cell markers (CD20+ and CD 20+/21+) indicating that it can effectively bind to the target and achieve the desired result of reducing the B-cell population.

Toxicology studies to support the chronic use of belimumab included 4-week (0, 5, 15, and 50 mg/kg/week) and 6-month (0, 5, 15 and 50 mg/kg every two weeks) intravenous (IV) studies in cynomolgus monkeys. In the 4-week study, the target organs of toxicity were the injection site, mesenteric lymph (lymphoid depletion), GI tract (lymphoid depletion), thyroid (follicular degeneration) and peripheral blood (B-cell depletion). In the 6-month IV study, the target organs of toxicity were the spleen (lymphoid depletion and hyperplasia), mesenteric lymph node (lymphoid depletion and hyperplasia), GI tract (lymphoid hyperplasia), kidney (regeneration of tubule and glomerular thickening), pancreas (mononuclear infiltration and fibrosis), and thyroid (mononuclear infiltration, follicular degeneration) and peripheral blood (B-cell decreased). Vasculitis was observed in a number of organs including the kidney, sciatic nerve, cervix, and heart with low incidence in females in the high-dose group (50 mg/kg). Most of these findings were considered as exaggerated pharmacological effect of the drug product with the exception of the observed vasculitis.

The reproductive toxicology program showed that belimumab did not affect male or female reproductive organs or female menstrual cyclicity with treatment up to 6-months. In the embryo-fetal and peri- and post-natal development study in monkeys, belimumab was shown to cross the placenta and was excreted in milk. There were fetal and infant deaths from the control (3 fetus and2 infants), low (6 fetus and 4 infants), and high dose group (1 fetus and 4 infants) animals, respectively. The low dose group deaths were increased compared to controls but no dose response was observed. The cause of deaths of the fetuses and infants are unknown.

The Clinical Pharmacology of Belimumab

Belimumab administered as an intravenous (IV) infusion in subjects with SLE has been studied in one Phase 1 trial (Study LBSL01), one Phase 2 trial (Study LBSL02) and two Phase 3 trials (Studies C1056 and C1057). Belimumab was also studied in healthy subjects to assess the absolute bioavailability of subcutaneous (SC) injection as compared to the IV 1-hour infusion (Study C1058). The proposed dosage regimen is 10 mg/kg at two week intervals for the first 3 doses and at 4 week intervals thereafter as an intravenous infusion over one hour.

Pharmacokinetics in Healthy Subjects

A single-dose bioavailability study was conducted in healthy subjects in Study C1058. In this study, belimumab was administered SC as a single injection or IV as a 1-hour infusion at a dose of 100 mg for the evaluation of absolute bioavailability. Following the administration of a single SC dose of belimumab to healthy subjects, mean maximum plasma concentration was observed approximately 5 days after dosing. The bioavailability of the 100 mg SC dose is about 67%. Consistent with PK parameters from other monoclonal antibodies, following 100 mg IV 1-hour infusion of belimumab, the volume of distribution of belimumab at steady-state was 63 mL/kg and systemic clearance was 3.3 mL/day/kg.

Pharmacokinetics in SLE patients

In the Phase 1 ascending-dose study (LBSL01), belimumab was administered by IV infusion over 2 hours as a single dose or 2 doses with 21 days apart in escalating doses of 1, 4, 10, and 20 mg/kg in SLE patients. The results from this study showed that the exposure (AUC and Cmax) of belimumab was dose-proportional in the SLE patients in the dose range studied.

Based upon the population estimates of the PK model specific to 10 mg/kg dosing in the Phase 3 population, the half-life of belimumab was 19.4 days and clearance was 3.2 mL/day/kg.

Pharmacokinetics in special populations

The effect of sex, age, and race on the PK of belimumab was assessed using the population approach, in which four studies (Studies LBSL01, LBSL02, C1056, C1057) were included for the population PK analysis.

Sex
Gender did not significantly influence belimumab pharmacokinetics in the largely (94%) female study population.

Age
Age did not significantly influence belimumab pharmacokinetics in the study population, where the majority of subjects (70%) were between 18 and 45 years of age. Belimumab has not been studied in the pediatric patients. Limited pharmacokinetic data are available in elderly patients.

Race
Race did not significantly influence belimumab pharmacokinetics. The racial distribution was 53% white/Caucasian, 16% Asian, 16% Alaska native/American Indian, and 14% black/African American.

Renal or Hepatic Impairment
No formal studies were conducted to examine the effects of renal or hepatic impairment on belimumab PK.

Immunogenicity

In the two phase 3 studies C1056 and C1057, 13.1% of SLE patients in 1 mg/kg and 0.9% of SLE patients in 10 mg/kg showed positive immunogenicity response (including both persistent and transient positive response). The presence of positive immunogenicity response did not appear to affect belimumab PK.

Summary of the Clinical Development Program

The investigational new drug application for belimumab was granted fast track status for the indication of SLE in March 2003. In April 2006, the FDA and the Sponsor held and end-of-phase 2 meeting where results of the failed Phase 2 study, LBSL02, were discussed and design elements for Phase 3 trials were agreed upon. After additional interim correspondence, the finalized protocols for the two pivotal trials HGS1006-C1056 and HGS1006-C1057 were submitted for special protocol assessment. These protocols included specific agreements on the target population, primary endpoint, concomitant medication plan, and statistical analysis plan. The Agency agreed to these protocols, stating that, "If results are positive from both the 76-week and 52-week proposed pivotal Phase 3 studies as they are currently designed, they could be used to support an indication similar to the one you proposed [reducing disease activity in adult patients with active, autoantibody positive systemic lupus erythematosus who are receiving standard therapy]." The Agency reiterated the expectation that Week 76

efficacy data should be submitted in the Biologic License Application (BLA) at the pre-BLA meeting in April 2010. A summary of the key design features of the trials that comprise the belimumab SLE clinical development program may be found in Table 2, below.

Table 2: Key Design Features of the Belimumab SLE Clinical Development Program Trials

Study/ Objectives	Study Design; Duration; No. of Study Sites	Dosage Regimen; Route of Administration	Number of Subjects	Diagnosis and Entry Criteria	Primary Endpoint (EP)
Phase 1					
Protocol LBSL01 **Objectives:** 1. Assess the safety tolerability, PK/PD and immunogenicity of intravenous belimumab in patients with SLE 2. Determine the effect of belimumab on clinical disease activity, serum immnoglobulins peripheral mature B lymphocytes and plasmacytoid cells and biological markers	Multicenter, randomized, double-blind, placebo controlled, single and double dose-escalation, tolerance, safety, PK/PD and immunogenicity trial 16 sites in U.S.	Belimumab 1, 4, 10, and 20 mg/kg via intravenous (IV) infusion (single infusions administered over 2 hours or 2 infusions 21 days apart) Placebo via IV infusion	N=70 57 subjects in Belimumab group (Cohorts 1-4 single dose: 29 subjects; Cohorts 5-8 double dose: 28 subjects) 13 subjects in placebo group	Adults age ≥ 18 years with SLE disease as defined by American College of Rheumatology (ACR) criteria that is active for at least 2 months prior to screening with history of measurable autoantibodies	Not Applicable
Protocol HGS1006-C1058 **Objectives:** 1. Determine the absolute bioavailability of belimumab administered via subcutaneous (SC) injection; 2. Assess the safety of SC vs IV belimumab	Multicenter, randomized, open label, parallel group, absolute bioavailability trial	Single dose of belimumab 100 mg via IV infusion over 1 hour Single dose of belimumab 100 mg via SC injection	N=36 17 subjects in belimumab IV group 19 subjects in belimumab SC group	Healthy volunteer adults	Not Applicable
Phase 2					
Protocol LBSL02 **Objectives:** 1. Determine the safety and tolerability of belimumab in subjects with SLE; 2. Assess the efficacy of belimumab in subjects with SLE	Multicenter, randomized, double-blind, placebo – controlled, dose ranging, 52-week, comparative parallel group, safety, tolerability, and efficacy trial with optional 24-week extension 57 sites in U.S. and 1 site in Canada	Belimumab 1, 4 and 10 mg/kg or placebo via IV infusion on Days 0, 14, 28 and every 28 days for 52 weeks of double blind portion. Optional 24 week extension: placebo patients switched to belimumab 10 mg/kg; others continue original dose if had satisfactory response or increased to 10 mg/kg of belimumab All subjects received concomitant SLE standard therapy	N=449 336 subjects in belimumab group 113 subjects in placebo group	Adults age ≥ 18 years with SLE as defined by ACR criteria that is active as per SELENA SLEDAI disease activity score ≥ 4 at screening with history of measurable autoantibodies	Two co-primary efficacy endpoints: 1. SELENA SLEDAI disease activity score at Week 24 and 2. Time to the 1st mild/moderate or sever flare (as defined by the SLE Flare Index) over 52 weeks

Table 2 Key Design Features of the Belimumab SLE Clinical Development Program Trials (continued)

Study/ Objectives	Study Design; Duration; Number of Study Sites	Dosage Regimen; Route of Administration	Number of Subjects	Diagnosis and Entry Criteria	Primary Endpoint (EP)
Phase 2					
Protocol HGS1006-C1070* **Objective:** Evaluate the safety, tolerability and PK of two doses of belimumab when administered via subcutaneous (SC) injection in subjects with SLE	Multicenter, randomized, open label, parallel group, 24-week trial with 144–week open-label continuation 10 sites U.S. and 1 site Mexico	Belimumab 100 mg SC on days 0, 7, 14 and then every 2 weeks Belimumab 200 mg SC on days 0, 2 , 4 and then 100 mg three times per week All subjects received concomitant SLE standard therapy	N=56 28 subjects every two weeks 28 subjects three times/week	Adults age ≥ 18 years with SLE as defined by ACR criteria that is active as per SELENA SLEDAI disease activity score ≥ 4 at screening with positive autoantibodies	Not Applicable
Phase 3					
Protocol HGS1006-C1056 (BLISS-76) **Objectives:** 1. Demonstrate the efficacy of belimumab in patients with SLE; 2. Assess the safety and tolerability of belimumab in patients with SLE; and 3. Determine the impact of belimumab on SLE patients' quality of life	Multicenter, randomized, double-blind, placebo-controlled, 76-week comparative parallel group trial 65 sites North America, 62 sites Europe and 9 sites Latin America	Belimumab 1 and 10 mg/kg and placebo via IV infusion on days 0, 14, 28 and then every 28 days for 72 weeks All subjects received concomitant SLE standard therapy	N=819 271 subjects belimumab 1mg/kg 273 subjects belimumab 10 mg/kg 275 subjects placebo	Adults age ≥ 18 years with SLE as defined by ACR criteria that is clinically active as per SELENA SLEDAI disease activity score ≥ 6 at screening, with positive ANA/anti-dsDNA test at 2 independent timepoints, on stable SLE treatment regimen for ≥ 30 days prior to Day 0. Individuals with severe active lupus nephritis or CNS lupus were prohibited	Response rate at Week 52 defined as the proportion of patients with: ≥ 4 point reduction from baseline in SELENA SLEDAI score AND no worsening (increase of < 0.30 points from baseline in PGA AND no new BILAG A organ domain score or 2 new BILAG B organ domain scores compared with baseline
Protocol HGS1006-C1057 (BLISS52) **Objectives:** 1. Demonstrate the efficacy of belimumab in patients with SLE; 2. Assess the safety and tolerability of belimumab in patients with SLE; and 3. Determine the impact of belimumab on SLE patients' quality of life	Multicenter, randomized, double-blind, placebo-controlled, 52-week comparative parallel group trial 41 sites Asian Pacific, 40 sites Latin America and 11 sites Europe	Belimumab 1 and 10 mg/kg and placebo via IV infusion on Days 0, 14, 28 and then every 28 days for 48 weeks All subjects received concomitant SLE standard therapy	N=865 288 subjects belimumab 1mg/kg 290 subjects belimumab 10 mg/kg 287 subjects placebo	Adults age ≥ 18 years with SLE as defined by ACR criteria that is clinically active as per SELENA SLEDAI disease activity score ≥ 6 at screening, with positive ANA/anti-dsDNA test at 2 independent timepoints, on stable SLE treatment regimen for ≥ 30 days prior to Day 0. Individuals with severe active lupus nephritis or CNS lupus were prohibited	Response rate at Week 52 defined as the proportion of patients with: ≥ 4 point reduction from baseline in SELENA SLEDAI score AND no worsening (increase of < 0.30 points from baseline in PGA AND no new BILAG A organ domain score or 2 new BILAG B organ domain scores compared with baseline

Table 2 Key Design Features of the Belimumab SLE Clinical Development Program Trials (continued)

Study/ Objectives	Study Design; Duration; Number of Study Sites	Dosage Regimen; Route of Administration	Number of Subjects	Diagnosis and Entry Criteria	Primary Endpoint (EP)
Open-Label Extension Studies					
Protocol LBSL99** **Objective:** Evaluate the long-term safety of subjects treated with belimumab	Multicenter, uncontrolled, open-label, 12-month continuation study of Protocol LBSL02 57 sites in U.S. and 1 site in Canada	Belimumab 10 mg/kg via IV infusion every 28 days	N=296	Subjects with SLE who had completed Protocol LBSL02 and had achieved a satisfactory response	Not Applicable
Protocol HGS1006-C1066** Objectives: Evaluate the long-term safety, efficacy and quality of life in subjects treated with belimumab	Multicenter, uncontrolled, open-label, continuation study of Protocol 1056 52 sites in U.S.	Belimumab 1 or 10 mg/kg via IV infusion every 28 days	Target enrollment: 428 subjects Enrollment as of 12/31/09: 233 subjects (85 subjects 1 mg/kg belimumab; 148 subjects 10 mg/kg belimumab)	Subjects with SLE who had completed Trial 1056 in the U.S.	Not Applicable
Protocol HGS1006-C1074** **Objectives:** Evaluate the long-term safety and SLICC damage assessments in subjects treated with belimumab	Multicenter, uncontrolled, open-label, continuation study of Protocol 1057 112 sites: 2 North America; 43 sites in EU; 36 sites S. America 31 sites Asia Pacific	Belimumab 1 or 10 mg/kg via IV infusion every 28 days	Target enrollment: 1265 subjects Enrollment as of 12/31/09: 712 subjects (235 subjects 1 mg/kg belimumab; 477 subjects 10 mg/kg belimumab)	Subjects with SLE who had completed Trial 1056 or 1057 in Canada, EU, S. America and Asia Pacific	Not Applicable

**Trials 1070, LBSL99, 1066 and 1074: Ongoing

The failed Phase 2 Study, LBSL02, was a 52-week randomized controlled trial in 449 SLE patients assessing belimumab at 1 mg/kg, 4 mg/kg or 10 mg/kg IV every 4 weeks vs. placebo. The primary endpoints for the study were percent change in SELENA-SLEDAI disease activity score at Week 24 and Time to First Mild/Moderate or Severe SLE Flare (as defined by the SELENA-SLEDAI SLE Flare index) over 52 weeks. In this study, belimumab treatment did not demonstrate a treatment effect for any of the primary or secondary endpoints. At Week 24, the mean percent decrease in SELENA SLEDAI score was 23% for the 1 mg/kg, 11% for the 4 mg/kg, and 20% for the 10 mg/kg belimumab treatment groups versus 17% for the placebo group. The median time to flare was 67 days for all belimumab groups versus 83 days for the placebo-treated patients. In post-hoc analyses, it was hypothesized that a belimumab treatment effect may have been present in the subgroup of patients who were autoantibody positive (i.e. ANA and/or anti-dsDNA), which represented 72% of the study population. Thus only autoantibody positive SLE patients were studied in the two pivotal trials 1056 and 1057.

As mentioned, Study 1056 and Study 1057 were the subject of Special Protocol Assessment (SPA) agreements. In particular, these agreements included the target

population to be studied, choice of the primary endpoint, concomitant medication controls (as related to impacting the primary endpoint) and statistical analysis plans. These studies utilized an identical study design but differed in duration of treatment (i.e., 76 weeks versus 52 weeks, respectively).

Study 1056 is a 76-week randomized, double-blind, placebo-controlled trial in 819 patients with active seropositive SLE on stable immunosuppressive medications. This study was conducted primarily in North America (65 centers) and Europe (62 centers). The remaining 9 centers were in Latin America. Active SLE was defined as a SELENA-SLEDAI disease activity score ≥6 at screening, and seropositivity was defined as an ANA of at least 1:80 titer and/or an anti-dsDNA of at least 30 IU/mL on at least 2 separate occasions. Patients were excluded if they had severe active lupus nephritis, CNS lupus, a history of treatment with targeted B-cell therapy, abatacept within 1 year, intravenous cyclophosphamide within 6 months, anti-TNF therapy, IV immunoglobulin (IVIG), prednisone at doses greater than 100 mg/day, plasmapheresis within 3 months, or live vaccine within 1 month of study entry. Patients were randomized via a 1:1:1 ratio stratified by screening SLENA SLEDAI score (6-9 vs >10), screening proteinuria level (<2 g/24 hours vs >2 g/24 hours equivalent) to 1 mg/kg belimumab IV, 10 mg/kg belimumab IV, or Placebo IV, given on Days 0, 14, 28, then every 28 days thereafter through Week 72.

The primary endpoint for the study was defined as proportion of responders at Week 52, where response is defined as:

- ≥4-point reduction in the SELENA-SLEDAI score compared to baseline, AND
- No worsening (i.e. increase <0.3 points from baseline) in physician global assessment (PGA) 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 major secondary endpoints for the study included:

- Proportion of patients achieving a response (as previously defined) at Week 76
- Percent of patients with >4 point reduction from baseline in SELENA SLEDAI score at Week 52
- Mean change in PGA at Week 24
- Mean change in SF-36 physical component summary score (PCS) at Week 24, and
- Proportion of patients who were able to reduce their average prednisone dose by at least 25% from baseline to ≤7.5 mg/day during Weeks 40 through 52.

Additional endpoints assessed included time-to-flare, rate of flares, other assessments of corticosteroid reduction, renal involvement, effects on biomarkers, and effects on various patient-reported outcomes. The protocols for studies 1056 and 1057 specified that a step-down sequential testing procedure would be used to account for multiplicity in doses in the analysis of the primary efficacy endpoint (i.e., comparison of belimumab 10 mg/kg to placebo was conducted first and only if that comparison was statistically significant was the comparison of belimumab 1 mg/kg to placebo to be conducted). The protocols did

not provide a multiplicity correction for multiple doses or multiple endpoints during the analyses of the major and/or additional secondary endpoints.

Study 1057 was an essentially replicate study in 810 SLE patients, with a shorter controlled period of 52-weeks. This study was conducted entirely outside the US, predominantly in Asia Pacific (41 centers) and Latin America (38 centers). The remaining 11 centers were in Europe. As will be discussed in further detail below, the evidence for belimumab's efficacy is strongest in Study 1057. The disparity between the results of 1056 and 1057 again raises the specter of the heterogeneity of SLE, and whether the disease entity in different populations is sufficiently similar such that extrapolation of efficacy is possible.

Review of Efficacy

Patient Population Characteristics

As summarized in the following tables (Tables 3 and 4), the treatment groups within the Phase 3 trials were generally well balanced with respect to baseline demographics, region, disease characteristics and activity.

The subjects who participated in Study 1056 were predominantly Caucasian (68%) and female (92%). Fourteen percent (14%) of the patients were of Black/African American in origin. The majority (53%) of subjects in Study 1056 were from the U.S. and Canada while the remaining subjects were from Western Europe/Israel (25%) and Eastern Europe (11%). The mean age of subjects was 40 years and mean weight of subjects was 73 kg. No important imbalances in these demographic factors across treatment groups were noted within study 1056. The population of Study 1057, which was conducted outside the U.S., was also predominantly female (94%) but unlike in study 1056 was comprised of 38% Asians 32% Native or American Indians, 27% Caucasians, and 4% Black/African American subjects. Patients in Study 1057 were also slightly younger (mean age 36 years) and weighed less (mean weight 61 kg) as compared to patients in Study 1056. The majority (50%) of subjects in Study 1057 were from Latin America while the remaining subjects were from Asia (38%) and Eastern Europe (11%). No important imbalances in these demographic factors across treatment groups were noted within study 1057.

Table 3: Baseline Demographics for Subjects in Studies 1056 and 1057

Demographics	1056				1057			
	Placebo (N=275)	Belimumab 1mg/kg (N=271)	Belimumab 10 mg/kg (N=273)	Total (N=819)	Placebo (N=287)	Belimumab 1mg/kg (N=288)	Belimumab 10 mg/kg (N=290)	Total (N=865)
Gender:								
Female	252 (92%)	253 (93%)	259 (95%)	**764 (93%)**	270 (94%)	271 (94%)	280 (97%)	**821 (95%)**
Male	23 (8%)	18 (7%)	14 (5%)	**55 (7%)**	5 (6%)	17 (6%)	10 (3%)	**44 (5%)**
Race[1]:								
Caucasian	188 (68%)	192 (71%)	189 (69%)	**569 (70%)**	82 (29%0	76 (26%)	71 (25%)	**229 (27%)**
Asian	11 (4%)	6 (2%)	11 (4%)	**28 (3%)**	105 (37%)	106 (37%)	116 (40%)	**327 (38%)**
Black/African Am.	39 (14%)	40 (15%)	39 (14%)	**118 (14%)**	11 (4%)	8 (3%)	11 (4%)	**30 (4%)**
Alaskan Nat./Am. Indian	36 (13%)	33 (12%)	34 (13%)	**103 (13%)**	89 (31%)	98 (34%)	92 (32%)	**279 (32%)**
Nat. Hawaiian/Pacific Isl.	1 (0%)	0 (0%)	0 (0%)	**1 (0%)**	0	0	0	**0**
Multiracial	2 (1%)	3 (1%)	3 (1%)	**8 (1%)**	1 (0%)	3 (1%)	1 (0%)	**5 (1%)**
Hispanic Origin:	55 (20%)	62 (23%)	56 (21%)	**173 (21%)**	143 (50%)	141 (49%)	136 (47%)	**420 (49%)**
Age (years):								
Mean (SD)	40 (12)	40 (11)	41 (11)	**40 (12)**	36 (12)	35 (11)	35 (11)	**36 (11)**
≤ 45	189 (69%)	184 (68%)	178 (65%)	**551 (67%)**	225 (78%)	236 (82%)	236 (81%)	**697 (81%)**
> 45 to <65	77 (28%)	83 (31%)	92 (34%)	**252 (31%)**	57 (20%)	48 (17%)	52 (18%)	**157 (18%)**
≥ 65 to <75	9 (3%)	4 (2%)	3 (1%)	**16 (2%)**	5 (2%)	4 (1%)	2 (1%)	**11 (1%)**
Weight:								
Mean (SD)	72 (18)	73 (18)	74 (21)	**73 (19)**	62 (12)	61 (13)	62 (13)	**61 (13)**
(Min, Max)	(43, 170)	(43, 136)	(45, 165)	**(43, 170)**	(35, 128)	(36, 120)	(36, 129)	**(35, 129)**
Region and Country								
USA/Canada	145 (53%)	155 (57%)	136 (50%)	**436 (53%)**	0	0	0	**0**
W. Europe/Israel	64 (23%)	63 (23%)	75 (28%)	**202 (25%)**	0	0	0	**0**
Eastern Europe	36 (13%)	27 (10%)	30 (11%)	**93 (11%)**	33 (12%)	34 (12%)	31 (11%)	**98 (11%)**
Americas (excl. USA/Canada)	30 (11%)	26 (10%)	32 (12%)	**88 (11%)**	0	0	0	**0**
Latin America	0	0	0	**0**	145 (51%)	143 (50%)	140 (48%)	**428 (50%)**
Asia	0	0	0	**0**	103 (36%)	106 (37%)	115 (40%)	**324 (38%)**
Australia	0	0	0	**0**	6 (2%)	5 (2%)	4 (1%)	**15 (2%)**

[1]Subjects who checked more than one race category are counted under individual race category according to the minority rule as well as multiracial category.
Adapted Sponsor's Table 6-3; p. 78 and Sponsor's Table T3; p. 449 of the study reports for Trials 1056 and 1057.

As shown in Table 4 below, the overall mean duration of SLE disease was 8 years for patients in Study 1056. Overall, these subjects had a high baseline level of disease activity as manifested by a SELENA SLEDAI mean score of 9.7 with 50% of the patients having a baseline SELENA SLEDAI score of ≥ 10 points. The individual treatment groups were similar in their baseline disease activity with only minor differences as assessed by the BILAG organ domain involvement, SELENA SLEDAI score category 0 to 3, and SLE flare index suggesting that patients with lower disease activity may have been slightly more frequently assigned to the belimumab 10mg/kg treatment group as compared to the placebo group. (Note: Patients with a baseline SELENA SLEDAI score category 0 to 3 were unable to achieve a response of ≥ 4 points necessary for a positive response as assessed by the primary endpoint, the SRI.)

In contrast to study 1056, subjects in Study 1057 had a shorter overall mean duration of SLE disease of 5.9 years. But similarly to study 1056, patients in this trial also had a high baseline level of disease activity as manifested by a SELENA SLEDAI mean score of 10 with 53% of the patients having a baseline SELENA SLEDAI score of ≥ 10 points. No

imbalances in baseline disease activity were observed for the three treatment groups in this trial.

Table 4: Baseline Disease Characteristics of Subjects in Studies 1056 and 1057

Characteristic	Trial 1056				Trial 1057			
	Placebo (N=275)	Belimumab 1mg/kg (N=271)	Belimumab 10 mg/kg (N=273)	Total (N=819)	Placebo (N=287)	Belimumab 1mg/kg (N=288)	Belimumab 10 mg/kg (N=290)	Total (N=865)
SLE Disease Durat. (yr): Mean (SD)	7 (7)	8 (7)	7 (8)	**8 (7)**	6 (6)	5 (5)	5 (5)	**5 (5)**
BILAG Organ Domain Involvement:								
At least 1A or 2B	187 (68%)	173 (64%)	160 (59%)	**520 (64%)**	166 (58%)	166 (58%)	172 (59%)	**504 (58%)**
At Least 1A	37 (14%)	38 (14%)	24 (9%)	**99 (12%)**	52 (18%)	58 (20%)	54 (19%)	**164 (19%)**
At Least 1A or 1B	258 (94%)	245 (90%)	251 (92%)	**754 (92%)**	259 (90%)	255 (89%)	258 (89%)	**772 (89%)**
No A or B	17 (6%)	26 (10%)	22 (8%)	**65 (8%)**	28 (10%)	33 (12%)	32 (11%)	**93 (11%)**
SELENA SLEDAI Category:								
0 to 3	3 (1%)	5 (2%)	8 (3%)	**16 (2%)**	1 (0%)	4 (1%)	3 (1%)	**8 (1%)**
4 to 9	131(48%)	122 (45%)	129 (47%)	**382 (47%)**	128 (45%)	145 (50%)	127 (44%)	**400 (46%)**
10 to 11	62(23%)	72 (27%)	65 (24%)	**199 (24%)**	75 (26%)	53 (18%)	72 (25%)	**200 (23%)**
≥ 12	79 (29%)	72 (27%)	71 (26%)	**222(27%)**	83 (29%)	86 (30%)	88 (30%)	**257 (30%)**
SELENA SLEDAI Score: Mean (SD)	9.8 (4.0)	9.7 (3.7)	9.5 (3.6)	**9.7 (3.8)**	9.7 (3.6)	9.6 (3.8)	10 (3.9)	**9.8 (3.8)**
SLE Flare Index[1]:								
At Least 1 Flare	82 (30%)	63 (23%)	59 (22%)	**204 (25%)**	57 (20%)	53 (18%)	56 (19%)	**166 (19%)**
Severe Flare	3 (1%)	1 (0%)	4 (2%)	**8 (1%)**	1 (0.3%)	5 (2%)	4 (1%)	**10 (1%)**
PGA Category:								
0 to 1	33 (12%)	39 (14%)	51 (19%)	**123 (15%)**	43 (15%)	38 (13%)	32 (11%)	**113 (13%)**
>1 to 2.5	239 (87%)	230 (85%)	219 (80%)	**688 (84%)**	243(85%)	247 (86%)	256 (88%)	**746 (86%)**
>2.5 to 3	3 (1%)	2 (1%)	3 (1%)	**8 (1%)**	1 (0%)	3 (1%)	2 (1%)	**6 (1%)**
PGA Scale: Mean (SD)	1.5 (0.47)	1.4 (0.50)	1.4 (0.54)	**1.4 (0.50)**	1.4 (0.48)	1.4 (0.47)	1.4 (0.45)	**1.4 (0.47)**
SLICC Damage Index Score Mean (SD)	0.99 (1.45)	1.04 (1.39)	0.94 (1.38)	**0.99 (1.41)**	0.55 (0.93)	0.60 (1.1)	0.55 (1.0)	**0.57 (1.0)**
Proteinuria Category (g/24 hr):								
<0.5	228 (83%)	231 (85%)	230 (84%)	**689 (84%)**	215 (755)	216 (75%)	220 (76%)	**651 (75%)**
0.5 to <1	24 (9%)	22 (8%)	13 (5%)	**59 (7%)**	20 (7%)	23 (8%)	22 (8%)	**65 (8%)**
1 to <2	12 (4%)	11 (4%)	15 (6%)	**38 (5%)**	31 (11%)	23 (8%)	29 (10%)	**83 (10%)**
≥ 2	11 (4%)	7 (3%)	15 (6%)	**33 (4%)**	21 (7%)	26 (9%)	19 (7%)	**66 (8%)**
Proteinuria Level (g/24 hr) Mean (SD)	0.39 (0.81)	0.33 (0.65)	0.4 (0.73)	**0.4 (0.74)**	0.62 (1.2)	0.63 (1.1)	0.54 (0.9)	**0.6 (1.1)**

[1]At baseline compared with screening assessment.
Adapted Sponsor's Table 6-4; p. . Adapted Sponsor's Table A81; p. 479.

As shown in Table 5 below, the majority of patients who participated in Study 1056 had musculoskeletal and/or mucocutaneous manifestations of SLE disease at baseline as assessed by the SELENA SLEDAI disease activity index. Baseline disease involvement was generally well balanced between the three treatment groups with the exception of rash. Higher proportions of placebo patients (68%) and patients in the 1mg/kg belimumab group (66%) had rash at study entry as compare to patients in the 10 mg/kg (56%). A similar pattern of SLE disease involvement at baseline was observed for subjects in Study 1057, however, a lower rate of arthritis (59%) was reported by subjects in this study as compared to Study 1056 (72%). Baseline disease involvement was also similar for all three treatment groups in this trial.

Table 5: Selected Baseline SELENA SLEDAI Scores for Subjects in Studies 1056 and 1057

Condition (weight)	Trial 1056				Trial 1057			
	Placebo (N=275)	Belimumab 1mg/kg (N=271)	Belimumab 10 mg/kg (N=273)	Total (N=819)	Placebo (N=287)	Belimumab 1mg/kg (N=288)	Belimumab 10 mg/kg (N=290)	Total (N=865)
Organic Brain Syndrome (8)	1 (0%)	2 (1%)	3 (1%)	**6 (1%)**	0	2 (1%)	0	**2 (1%)**
Lupus HA (8)	1 (0%)	4 (2%)	9 (3%)	**14 (2%)**	4 (1%)	2 (1%)	4 (1%)	**10(1%)**
Vasculitis (8)	17 (6%)	20 (7%)	10 (4%)	**47 (6%)**	20 (7%)	16 (6%)	28 (10%)	**64 (7%)**
Arthritis (4)	206 (75%)	193 (71%)	191 (70%)	**590 (72%)**	165 (58%)	169 (59%)	173 (60%)	**507 (59%)**
Hematuria (4)	5 (2%)	7 (3%)	8 (3%)	**20 (2%)**	15 (5%)	16 (6%)	16 (6%)	**47(5%)**
Proteinuria (4)	29 (11%)	23 (9%)	26 (10%)	**78 (10%)**	50 (19%)	54(19%)	41 (14%)	**145 (17%)**
Rash (2)	187 (68%)	180 (66%)	154 (56%)	**521 (64%)**	176 (61%)	176 (61%)	182 (63%)	**534 (62%)**
Alopecia (2)	130 (47%)	137 (51%)	116 (43%)	**383 (47%)**	150 (52%)	138 (48%)	158 (55%)	**446 (52%)**
Mucosal Ulcers (2)	74 (27%)	57 (21%)	78 (29%)	**209 (26%)**	71 (25%)	52 (18%)	58 (20%)	**181 (21%)**
Low Complement (2)	160 (58%)	149 (55%)	159 (58%)	**468 (57%)**	183 (64%)	186 (65%)	198 (68%)	**567 (66%)**
Inc. DNA Binding (2)	175 (64%)	168 (62%)	176 (65%)	**519 (63%)**	205 (71%)	220 (76%)	218 (75%)	**643 (74%)**
Leukopenia (1)	16 (6%)	22 (8%)	23 (8%)	**61 (7%)**	18 (6%)	12 (4%)	9 (3%)	**39 (5%)**

Modified Sponsor's Table T20

A summary of moderate to severe BILAG organ system involvement (A or B score) at baseline for both pivotal trials is displayed in Table 6 below. The most common organ systems involved in subjects participating in Study 1056 were musculoskeletal (67%), mucocutaneous (58%) and hematology (14%). The three treatment groups in this trial were generally well balanced for baseline organ involvement with the exception of slight differences in the rate of musculoskeletal involvement. A similar pattern for moderate to severe organ involvement that was generally balanced across the three treatment groups was observed for subjects participating in Study 1057, however, a lower rate of musculoskeletal involvement (42%) and a higher rate of renal involvement (13%) were reported by patients in this trial as compared to patients in Study 1056 (67% and 7%, respectively).

Table 6: Summary of Baseline BILAG Category by Organ Domain for Subjects in Studies 1056 and 1057.

BILAG Organ Domain Category	Trial 1056				Trial 1057			
	Placebo (N=275)	Belimumab 1mg/kg (N=271)	Belimumab 10 mg/kg (N=273)	Total (N=819)	Placebo (N=287)	Belimumab 1mg/kg (N=288)	Belimumab 10 mg/kg (N=290)	Total (N=865)
Cardiovascular & Respiratory								
With A	2 (1%)	2 (1%)	1 (0%)	**5 (1%)**	2 (1%)	3 (1%)	1 (0%)	**6 (1%)**
With B	7 (3%)	11 (4%)	14 (5%)	**32 (4%)**	10 (4%)	3 (1%)	5 (2%)	**18 (2%)**
General								
With A	2 (1%)	1 (0%)	0 (0%)	**3 (0%)**	3 (1%)	0 (0%)	3 (1%)	**6 (1%)**
With B	36 (13%)	29 (11%)	38 (14%)	**103 (13%)**	25 (9%)	23 (8%)	23 (8%)	**71 (8%)**
Hematology								
With A	0 (05)	0 (0%)	1 (0%)	**1 (0%)**	1 (0%)	2 (1%)	3 (1%)	**6 (1%)**
With B	36 (13%)	40 (15%)	34 (13%)	**110 (13%)**	51 (18%)	54 (19%)	50 (17%)	**155(18%)**
Mucocutaneous								
With A	15 (6%)	16 (6%)	12 (4%)	**43 (5%)**	9 (3%)	12 (4%)	10 (3%)	**31 (4%)**
With B	163 (59%)	143 (53%)	129 (47%)	**435(53%)**	163 (57%)	155 (54%)	164 (57%)	**482(56%)**
Musculoskeletal								
With A	14 95%)	11 (4%)	10 (4%)	**35 (4%)**	33 (12%)	33 (12%)	25 (9%)	**91 (11%)**
With B	181 (66%)	166 (61%)	169 (62%)	**516 (63%)**	114 (40%)	117 (41%)	135 (47%)	**366(42%)**
Neurological								
With A	0 (0%)	3 (1%)	1 (0%)	**4 (1%)**	0 (0%)	0 (0%)	0 (0%)	**0 (0%)**
With B	6 (2%)	4 (2%)	6 (2%)	**16 (2%)**	0 (0%)	1 (0%)	0 (0%)	**1 (0%)**
Renal								
With A	0 (0%)	1 (0%)	1 (0%)	**2 (0%)**	1 (0%)	5 (2%)	2 (1%)	**8 (1%)**
With B	21 (8%)	13 (5%)	23 (8%)	**57 (7%)**	37 (13%)	43 (15%)	32 (11%)	**112(13%)**
Vasculitis								
With A	7 (3%)	9 (3%)	3 (1%)	**19 (2%)**	7 (2%)	7 (2%)	16 (6%)	**30 (4%)**
With B	23 (8%)	14 (5%)	15 (6%)	**52 (6%)**	15 (5%)	18 (6%)	17 (6%)	**50 (6%)**

The vast majority (96-98%) of patients in these trials were seropositive for ANA and/or anti-dsDNA as shown in Table 7 below. The treatment groups within each of the Phase 3 trials were generally well balanced with respect to baseline biomarkers of disease activity with the following exceptions. Differences in the 3 treatment groups for Study 1056 were observed for the presence of CRP, anti-ribosomal P and aCL. Higher proportions of patients in the placebo group of Study 1056 were positive for CRP (42%) and anti-ribosomal P (11%) as compared to the belimumab treatment groups (1 mg/kg group: 37% and 5%; 10 mg/kg group: 33% and 6%, respectively). Additionally, the proportions of subjects who were positive for CRP were higher in the 1 mg/kg belimumab treatment group (46%) as compared to the belimumab 10mg/kg (37%) and placebo (36%) groups. Overall, higher proportions of patients in Study 1057 were seropositive for anti-ribosomal P (26%) and anti-Smith (36%) as compared to Study 1056 (7% and 27%, respectively).

Table 7: Tabular Summary of Subjects' Baseline Serologies, Immunoglobulins, Complement, and Other Biomarkers for Trials 1056 and 1057

Biomarkers	Trial 1056				Trial 1057			
	Placebo (N=275)	Belimumab 1mg/kg (N=271)	Belimumab 10 mg/kg (N=273)	Total (N=819)	Placebo (N=287)	Belimumab 1mg/kg (N=288)	Belimumab 10 mg/kg (N=290)	Total (N=865)
Anti-dsDNA:								
Positive (≥ 30 IU/mL)	174 (63%)	171 (63%)	179 (66%)	**524 (64%)**	205 (71%)	221 (77%)	218 (75%)	**644 (75%)**
Mean (SD)	151 (66)	139 (63)	143 (62)	**144 (62)**	144 (64)	146 (62)	144 (62)	**145 (62)**
ANA[1]:								
Positive (≥ 80 Titer)	253 (92%)	256 (95%)	245 (90%)	**754 (92%)**	264 (92%)	272 (94%)	276 (95%)	**812 (94%)**
Mean (SD)	836 (493)	850 (478)	796 (488)	**828 (486)**	881 (466)	851 (483)	903 (476)	**878 (475)**
ANA and/or Anti-dsDNA Positive:	265 (96%)	262 (97%)	261 (96%)	**788 (96%)**	280 (98%)	281 (98%)	284 (98%)	**845 (98%)**
aCL[2]:								
Positive	116 (42%)	101 (37%)	88 (33%)	**305 (37%)**	88 (31%)	106 (37%)	111 (39%)	**305 (35%)**
Anti-ribosomal P:								
Positive (>25 EU/mL)	29 (11%)	14 (5%)	15 (6%)	**58 (7%)**	80 (29%)	79 (28%)	62 (22%)	**221 (26%)**
Mean (SD)	67 (41)	70 (39)	66 (42)	**67 (40)**	73 (36)	66 (36)	67 (37)	**69 (36)**
Anti-Smith:								
Positive(≥ 15 U/mL)	72 (27%)	69 (26%)	75 (28%)	**216 (27%)**	101 (355)	102 (35%)	105 (37%)	**308 (36%)**
Mean (SD)	937 (5128)	1042 (4275)	478 (1941)	**811 (3978)**	1152 (4547)	438 (1276)	505 (1471)	**695 (2847)**
IgG:								
Mean (SD)	15.9 (6.1)	15.8 (6.6)	15.3 (6.0)	**15.7 (6.2)**	17.2 (6.0)	174 (6.2)	17.2 (5.6)	**17.3 (5.9)**
>ULN (16.18 g/L)	108 (39%)	105 (39%)	94 (34%)	**307 (38%)**	146 (51%)	140 (49%)	151 (52%)	**437 (51%)**
<LLN 6.94 g/L	6 (2%)	5 (2%)	6 (2%)	**17 (2%)**	1 (0%)	0 (0%)	3 (1%)	**4 (0%)**
IgA:								
Mean (SD)	3.0 (1.5)	2.9 (1.5)	3.0 (1.5)	**3.0 (1.5)**	3.1 (1.3)	3.3 (1.4)	3.2 (1.4)	**3.2 (1.4)**
>ULN (4.63 g/L)	38 (14%)	30 (11%)	37 (14%)	**105 (13%)**	33 (12%)	40 (14%)	36 (12%)	**109 (13%)**
<LLN (0.81 g/L)	6 (2%)	3 (1%)	5 (2%)	**14 (2%)**	2 (1%)	3 (1%)	7 (2%)	**12 (1)**
IgM:								
Mean (SD)	1.1 (0.7)	1.1 (0.7)	1.2 (0.9)	**1.1 (0.7)**	1.2 (0.8)	1.1 (0.7)	1.2 (0.7)	**1.2 (0.7)**
>ULN (2.71 g/L)	4 (1%)	10 (4%)	16 (6%)	**30 (4%)**	12 (4%)	10 (4%)	9 (3%)	**31 (4%)**
<LLN (0.48 g/L)	41 (15%)	38 (14%)	37 (14%)	**116 (14%)**	37 (13%)	32 (11%)	33 (11%)	**102 (12%)**
C3:								
Mean (SD)	958 (303)	995 (321)	973 (325)	**975 (317)**	938 (313)	898 (303)	917 (321)	**918 (313)**
Low (<900 mg/L)	116 (42%)	100 (37%)	115 (42%)	**331 (40%)**	132 (46%)	148 (51%)	147 (51%)	**427 (49%)**
C4:								
Mean (SD)	16 (9)	17 (10)	16 (10)	**17 (10)**	16 (10)	15 (9.4)	15 (10)	**16 (9.7)**
Low (<16 mg/dL)	143 (52%)	141 (52%)	147 (54%)	**431 (53%)**	160 (56%)	173 (60%)	180 (62%)	**513 (59%)**
CRP:								
Positive (>3 mg/L)	92 (35%)	123 (46%)	97 (37%)	**312 (39%)**	114(41%)	119 (42%)	119 (42%)	**352 (41%)**
Mean (SD)	15 (20.0)	13 (15.5)	11 (11.0)	**13 (15.7)**	13 (17.7)	12 (12.5)	12 (11.9)	**12 (14.2)**
BLyS:								
Above LOQ	268 (99%)	267 (99%)	263 (98%)	**798 (99%)**	272 (97%)	272 (96%)	281 (99%)	**827 (97%)**
Mean (SD)	1.7 (1.5)	1.8 (1.3)	1.8 (1.5)	**1.8 (1.4)**	1.8 (1.5)	1.8 (1.6)	1.8 (2.8)	**1.8 (2.0)**

[1]ANA titer equals to the maximum titer of the individual patterns
[2]aCL is positive if any of aCL-IgG, aCL-IgA, or aCL-IgM is positive
Adapted Sponsor's Table 6-6; p. 82-83 Clinical Study C1056 Report and Sponsor's Table 6-6; p. 78 Clinical Study C1057 Report.

The following table (Table 8) summarizes concomitant SLE medications used by more than 10% of subjects who participated in the Phase 3 trials. The usage of concomitant SLE medications at baseline was generally similar for the three treatment groups each of these studies; however, there were major differences in the overall use of concomitant glucocorticosteroids, immunosuppressives and NSAIDs observed between trials. The overall concomitant use of glucocorticosteroids was considerably higher in Study 1057

(96%) as compared to Study 1056 (76%) with 24% of the patients in Study 1056 reportedly not taking concomitant prednisone or equivalent at baseline as compared to only 4% of patients in Study 1057. More subjects (69%) in Study 1057 were also taking >7.5 mg/day of prednisone or equivalent at baseline as compared to 46% of subjects in Study 1056. In contrast, the overall use of immunosuppressives (56%) and NSAIDs (41%) by patients in Study 1056 was higher as compared to patients in Study 1057 (42% and 20%, respectively).

Table 8: Concomitant SLE Medication Usage by >10% of Subjects at Baseline in Studies 1056 and 1057

SLE Medications	Trial 1056				Trial 1057			
	Placebo (N=275)	Belimumab 1mg/kg (N=271)	Belimumab 10 mg/kg (N=273)	Total (N=819)	Placebo (N=287)	Belimumab 1mg/kg (N=288)	Belimumab 10 mg/kg (N=290)	Total (N=865)
Total Glucocorticoid Use:	212 (77%)	211 (78%)	200 (73%)	**623 (76%)**	276 (96%)	276 (96%)	278 (96%)	**830 (96%)**
Methylprednisolone	37 (14%)	28 (10%)	35 (13%)	**100 (12%)**	46 (16%)	55 (19%)	52 (18%)	**153 (18%)**
Prednisolone	33 (12%)	35 (13%)	35 (13%)	**103 (13%)**	132 (46%)	123 (43%)	127 (44%)	**382 (44%)**
Prednisone	141 (51%)	147 (54%)	126 (46%)	**414 (51%)**	86 (30%)	88 (31%)	91 (31%)	**265 (31%)**
Prednisone or Equivalent Dose at Baseline:								
0 mg/day	63 (23%)	60 (22%)	73 (27%)	**196 (24%)**	11 (4%)	12 (4%)	12 (4%)	**35 (4%)**
>0 - ≤ 7.5 mg/day	86 (31%)	81 (30%)	80 (29%)	**247 (30%)**	84 (29%)	72 (25%)	74 (26%)	**230 (27%)**
>7.5 mg/day	126 (46%)	130 (48%)	120 (44%)	**376 (46%)**	192 (67%)	204 (71%)	204 (70%)	**600 (69%)**
Average Prednisone or Equival. Dose at Baseline:								
Mean (SD)	9 (9)	9 (8)	8.4 (8)	**9 (8)**	12 (8)	13 (9)	13 (10)	**13 (9)**
Angiotensin Pathway Antihypertensives:	68 (25%)	67 (25%)	71 (26%)	**206 (26%)**	61 (21%)	49 (17%)	72 (25%)	**182 (21%)**
Antimalarials:	180 (66%)	171 (63%)	168 (62%)	**519 (63%)**	201 (70%)	195 (68%)	185 (64%)	**581(67%)**
Immunosuppressives:	154 (56%)	153 (57%)	148 (54%)	**455 (56%)**	122 (43%)	120 (42%)	123 (42%)	**365 (42%)**
Azathioprine	57 (21%)	52 (19%)	58 (21%)	**167 (20%)**	67 (23%)	71 (25%)	84 (29%)	**222 (26%)**
Methotrexate	59 (22%)	53 (20%)	38 (14%)	**150 (18%)**	35 (12%)	24 (8%)	20 (7%)	**79 (9%)**
Mycophenolate	37 (14%)	44 (16%)	44 (16%)	**125 (15%)**	19 (7%)	15 (5%)	17 (6%)	**52 (6%)**
NSAIDs	119 (43%)	114 (42%)	101 (37%)	**334 (41%)**	59 (21%)	56 (19%)	58 (20%)	**173 (20%)**
HMG CoA Reductase Inhibitors	30 (11%)	25 (9%)	28 (10%)	**83 (10%)**	16 (6%)	13 (5%)	16 (6%)	**45 (5%)**

Adapted Sponsor's Table 6-7; p. 85. Adapted Sponsor's Table T19; p. 474.

Patient Disposition

As shown in Table 9 below, overall, the proportions of patients who discontinued from the three treatment arms of these studies were similar with just a slightly higher rate of early discontinuation occurring in the placebo groups than belimumab groups in each trial. A similar proportion of patients discontinued from these studies due to adverse events and lack of efficacy in the placebo and belimumab treatment groups. Of note, a higher number of patients were withdrawn from Study 1057 due to pregnancy.

Table 9: Subject Disposition in Trials 1056 and 1057

	Trial 1056				Trial 1057			
	Placebo	Belimumab 1mg/kg	Belimumab 10 mg/kg	Total	Placebo	Belimumab 1mg/kg	Belimumab 10 mg/kg	Total
Patients Randomized	277	275	274	**826**	288	289	290	**867**
Patients Treated (mITT)	275	271	273	**819**	287	288	290	**865**
Patients Who Completed Week 52:	205 (75%)	216 (80%)	209 (77%)	**630 (77%)**	226 (79%)	240 (83%)	241 (83%)	**707 (82%)**
Patients Withdrawn Before Week 52:	70 (26%)	55 (20%)	64 (23%)	**189 (23%)**	61 (21%)	48 (17%)	49 (17%)	**158 (18%)**
Subject Request	24 (9%)	14 (5%)	13 (5%)	**51 (6%)**	7 (2%)	6 (2%)	3 (1%)	**16 (2%)**
Adverse Event	16 (6%)	13 (5%)	19 (7%)	**48 (6%)**	19 (7%)	16 (6%)	15 (5%)	**50 (6%)**
Lack of Efficacy	15 (6%)	12 (4%)	14 (5%)	**41 (5%)**	16 (6%)	12 (4%)	12 (4%)	**40 (5%)**
Non-Compliance	2 (1%)	1 (0%)	2 (1%)	**5 (1%)**	1 (0%)	1 (0%)	1 (0%)	**3 (0%)**
Lost to Follow-Up	3 (1%)	4 (2%)	6 (2%)	**13 (2%)**	4 (1%)	6 (2%)	3 (1%)	**13 (2%)**
Protocol Violation	5 (2%)	2 (1%)	5 (2%)	**12 (2%)**	7 (2%)	2 (1%)	3 (1%)	**12 (1%)**
Invest. Decision	2 (1%)	3 (1%)	3 (1%)	**8 (1%)**	3 (1%)	2 (1%)	3 (1%)	**8 (1%)**
Other	3 (1%)	6 (2%)	2 (1%)	**11 (1%)**	4 (1%)	3 (1%)	9 (3%)	**16 (2%)**
Pregnancy[1]	-	2 (1%)	1 (0%)	**3 (0%)**	4 (1%)	3 (1%)	8 (3%)	**15 (2%)**

[1]Includes Subjects MX003-003 and MX008-009 in the 1mg/kg group and Subject US041-017 in the 10mg/kg group. In addition, Subject US061-002 in the 10 mg/kg group was pregnant and lost to follow-up and Subject MX007-001 in the 1 mg/kg group discontinued treatment due to pregnancy after Week 52.

Efficacy Results

Primary Endpoint

As discussed in the Background section above, the primary endpoint for both of the Phase 3 trials was the SRI response rate at Week 52. Using the SRI, a positive response defined as a:

- $\geq$ 4 point reduction from baseline in SELENA SLEDAI score AND
- No worsening (increase of <0.30 points from baseline) in the Physician's Global Assessment (PGA) AND
- No new BILAG A organ domain score or 2 new BILAG B organ domain scores compared with baseline at the time of assessment (i.e., at Week 52)

Subjects whose background SLE medications were changed after prespecified time points in the common protocol were imputed as treatment failures/nonresponders, as were subjects who dropped out or who had missing data for the Week 52 analysis. A step-down sequential testing procedure was used to account for multiplicity in doses in the analysis of the primary efficacy endpoint (i.e., comparison of belimumab 10 mg/kg to placebo was conducted first and only if that comparison was statistically significant was the comparison of belimumab 1 mg/kg to placebo to be conducted). The modified intent-to-treat (mITT) population was used for the primary analysis for each trial. This was defined as the subset of all randomized patients who received at least 1 dose of study agent. The mITT analysis was performed according to the treatment that a subject was randomized to receive, regardless of actual treatment received.

As shown in Table 10, patients treated with belimumab 10 mg/kg had a statistically higher rate of response than placebo patients in both Studies 1056 and 1057. A statistically higher rate of response for the belimumab 1 mg/kg group as compared to placebo was demonstrated for only study 1057. The results from the analyses of the subcomponents of the SRI were generally consistent with those of the primary analysis. The proportions of subjects achieving success for each of the subcomponents of the SRI were numerically higher in the belimumab groups than the placebo group in each study, although these differences only reached statistical significance for the belimumab 10 mg/kg to placebo comparison in Study 1057.

Table 10: Primary Efficacy Analyses (Adjusted, Week 52) for Trials 1056 and 1057

	Trial 1056			Trial 1057		
	Placebo (N=275)	**Belimumab 1mg/kg (N=271)**	**Belimumab 10 mg/kg (N=273)**	**Placebo (N=287)**	**Belimumab 1mg/kg (N=288)**	**Belimumab 10 mg/kg (N=290)**
Response:	93 (34%)	110 (41%)	118 (43%)	125 (44%)	148 (51%)	167 (58%)
Observed Difference vs PLO		7%	9%		8%	14%
OR (95% CI)[1] vs PLO		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)[1] vs PLO		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)[2] vs PLO		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 1A/2B BILAG Domain Scores:	179 (65%)	203 (75%)	189 (69%)	210 (73%)	226 (79%)	236 (81%)
OR (95% CI)[3] vs PLO		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**

PLO= Placebo; OR=Odds Ratio; CI =Confidence Interval
[1]OR (95% CI) and p-value were from logistic regression for the comparison between each belimumab dose and placebo with covariates including baseline SELENA SLEDAI (≤ 9 vs ≥ 10), baseline proteinuria level (<2 g/24 hour equivalent) and race (AIA vs other)
[2]OR (95% CI) and p-value were from logistic regression for the comparison between each belimumab dose and placebo with covariates as in footnote 1 and baseline PGA
[3]OR (95% CI) and p-value were from logistic regression for the comparison between each belimumab dose and placebo with covariates as in footnote 1 and baseline BILAG domain involvement (at least 1A/2B vs at most 1B)

Table 11 provides the reasons subjects failed to achieve a positive SRI response in these trials. Note that the categories provided are mutually exclusive and mutually exhaustive. The proportions of subjects who dropped out are approximately 16% in study 1056 and 12% in study 1057 and are fairly balanced across treatment groups within each study thus the impact of imputing dropouts as failures on the treatment effect in the primary analysis should be small. However, unlike dropouts, "medication failures" are not balanced across treatment groups (17%, 9%, and 10% for placebo, 1 mg/kg belimumab, and 10 mg/kg belimumab respectively in study 1056 and 11%, 7%, and 6% for the same in study 1057). Since medication failures are more frequent in the placebo groups than the belimumab groups, imputing medication failures as efficacy failures could bias the treatment effect in the primary efficacy endpoint in favor of belimumab (unless these subjects would truly have been unable to achieve success on the primary endpoint had they not taken the prohibited medication).

Table 11: Disposition of Patients in the Primary Efficacy Analyses for Trials 1056 and 1057

	Trial 1056			Trial 1057		
	Placebo (N=275)	Belimumab 1mg/kg (N=271)	Belimumab 10 mg/kg (N=273)	Placebo (N=287)	Belimumab 1mg/kg (N=288)	Belimumab 10 mg/kg (N=290)
Response:	93 (34%)	110 (41%)	118 (43%)	125 (44%)	148 (51%)	167 (58%)
No Response:	182 (66%)	161 (59%)	155 (57%)	162 (56%)	140 (49%)	123 (42%)
Dropout[1] – Not a Medication Failure	43 (16%)	40 (15%)	45 (17%)	38 (13%)	34 (12%)	31 (11%)
Medication Failure[2]	47 (17%)	24 (9%)	27 (10%)	30 (11%)	21 (7%)	18 (6%)
<4 Point Reduction in SELENA SLEDAI (SS)[3]	87 (32%)	91 (34%)	73 (27%)	87 (30%)	80 (28%)	72 (25%)
≥4 Point Reduction in SS with the following[3]:	5 (2%)	6 (2%)	10 (4%)	7 (2%)	5 (2%)	2 (1%)
Worsening in PGA only[3]	4 (2%)	4 (2%)	4 (2%)	5 (2%)	3 (1%)	1 (0%)
New 1A/2B/BILAG only[3]	1 (0%)	2 (1%)	6 (2%)	2 (1%)	2 (1%)	1 (0%)
Both Worsening in PGA and New 1A/2B BILAG[3]	--	--	--	--	--	--

[1]Subjects who withdrew early and had no data in the Day 364 +/- 28 day window
[2]Includes subjects who withdrew early and subjects who met all 3 response criteria at week 52 but took a protocol prohibited or restricted medication or dose
[3]In subjects who did not dropout and were not medication failures.

Table 12 provides sensitivity analyses designed to aid in addressing the issue of the medication failures. The first set of rows in table 12 includes the protocol-specified primary efficacy analysis as conducted by the FDA. (After careful review, the reasons for the small numerical differences in the results of the protocol-specified primary efficacy analyses conducted by the sponsor (Table 10) and FDA (Table 12) remain unclear.) The second set of results show the primary efficacy analysis ignoring the fact that prohibited medications were taken by some subjects, that is the data is used as it was observed or otherwise imputed (e.g., dropouts continue to be imputed as failures). The final analysis in Table 12 assigns the primary efficacy outcome for subjects who are medication failures post-hoc according to the judgment of the FDA medical team. The primary endpoint for subjects using prohibited medication other than HMG CoA Reductase Inhibitors or Angiotensin Pathway Antihypertensives were assigned as per-protocol (i.e., failures). The primary endpoint for subjects using HMG CoA Reductase Inhibitors or Angiotensin Pathway Antihypertensives was assigned as a success for the placebo subjects and a failure for the Belimumab subjects. Motivation for this imputation scheme was to take a very conservative approach for medication failure subjects who the clinical team did not feel would have unquestionably proceeded to be an efficacy failure had they not received the prohibited medication.

As expected since the frequency of medication failures is lower in study 1057 than study 1056 and since the primary efficacy result is stronger in study 1057 than study 1056, the sensitivity analyses of study 1057 are generally consistent with and supportive of the primary efficacy analysis for that study while they are not necessarily so for study 1056. In study 1056 the statistical significance of the comparison of 10 mg/kg belimumab to placebo is marginalized by the sensitivity analyses suggesting that the treatment effect shown in the primary efficacy results for that study is dependent on the disproportional occurrence of medication failures. Even as the apparently higher need for prohibited medication in the placebo group may be taken as a signal of efficacy for belimumab, the clinical importance of taking a prohibited medication relative to the clinical importance

of the primary efficacy endpoint should be evaluated and kept in mind in interpreting the primary efficacy results.

Table 12: Medication Failure Sensitivity Analyses of the Primary Efficacy Endpoint (Adjusted, Week 52) for Trials 1056 and 1057

	Trial 1056			Trial 1057		
	Protocol-Specified Primary Efficacy Analysis[1] (FDA Analysis)					
	Placebo (N=275)	Belimumab 1mg/kg (N=271)	Belimumab 10 mg/kg (N=273)	Placebo (N=287)	Belimumab 1mg/kg (N=288)	Belimumab 10 mg/kg (N=290)
Response:	93 (34%)	110 (41%)	118 (43%)	125 (44%)	148 (51%)	167 (58%)
Observed Difference vs PLO		7%	9%		8%	14%
OR (95% CI)[1] vs PLO		1.34 (0.95, 1.92)	1.51 (1.06, 2.15)		1.52 (1.08, 2.14)	1.82 (1.29, 2.56)
P-value		**0.0996**	**0.0215**		**0.0170**	**0.0006**
	Subjects with Medication Failure Analyzed as Observed[2] (FDA Analysis)					
	Placebo (N=275)	Belimumab 1mg/kg (N=271)	Belimumab 10 mg/kg (N=273)	Placebo (N=287)	Belimumab 1mg/kg (N=288)	Belimumab 10 mg/kg (N=290)
Response:	103 (37%)	117 (43%)	124 (45%)	130 (45%)	149 (52%)	171 (59%)
Observed Difference vs PLO		6%	8%		7%	14%
OR (95% CI)[1] vs PLO		1.28 (0.90, 7.81)	1.41 (1.00, 1.99)		1.44 (1.02, 2.03)	1.80 (1.28, 2.55)
P-value		**0.1691**	**0.0530**		**0.0379**	**0.0008**
	Subjects with Medication Failure Analyzed using Post-hoc Assignment by FDA Medical Team[3] (FDA Analysis)					
	Placebo (N=275)	Belimumab 1mg/kg (N=271)	Belimumab 10 mg/kg (N=273)	Placebo (N=287)	Belimumab 1mg/kg (N=288)	Belimumab 10 mg/kg (N=290)
Response:	99 (36%)	110 (41%)	118 (43%)	129 (45%)	148 (51%)	167 (58%)
Observed Difference vs PLO		5%	7%		6%	13%
OR (95% CI)[1] vs PLO		1.22 (0.86, 1.73)	1.37 (0.97, 1.94)		1.43 (1.01, 2.01)	1.71 (1.22, 2.41)
P-value		**0.2717**	**0.0775**		**0.0412**	**0.002**

PLO= Placebo; OR=Odds Ratio; CI =Confidence Interval
[1]OR (95% CI) and p-value were from logistic regression for the comparison between each belimumab dose and placebo with covariates including baseline SELENA SLEDAI ($\leq$ 9 vs $\geq$ 10), baseline proteinuria level (<2 g/24 hour equivalent) and race (AIA vs other). Subjects who received prohibited medication are imputed as failures.
[2]Use of prohibited medication ignored (i.e., treatment failure subjects were included in the analysis as their data was observed)
[3]Primary endpoint for subjects using prohibited medication other than HMG CoA Reductase Inhibitors or Angiotensin Pathway Antihypertensives were assigned as per-protocol (i.e., failures). The primary endpoint for subjects using HMG CoA Reductase Inhibitors or Angiotensin Pathway Antihypertensives was assigned as a success for the placebo subjects and a failure for the Belimumab subjects. Selection of the medication categories, HMG CoA Reductase Inhibitors and Angiotensin Pathway Antihypertensives, for this analysis was made post-hoc by the FDA medical team.

The sponsor provided four sensitivity analyses for the primary efficacy endpoint. These sensitivity analyses were conducted as planned in the protocol. The results of these sensitivity analyses are largely consistent with the primary efficacy analysis and are shown in Table 13. The first analysis, referred to as "unadjusted response" uses identical methods to the primary efficacy analysis with the exception that the logistic regression model does not include the stratification factors for randomization as independent variables. The results of this analysis are very similar to the primary efficacy results indicating that the estimated treatment effect was not overly influenced by the stratification factors. The second sensitivity analysis, the "LOCF response" differed from the primary efficacy analysis in the handling of subjects who were dropouts and not medication failures. Rather than imputing results for these subjects as efficacy failures as was done in the primary efficacy analysis, for this sensitivity analysis, a LOCF approach

was taken for imputation of these subjects' data. As should be expected since fewer failures are being imputed, the success rates using this analysis are slightly higher in all treatment groups than those from the primary efficacy analysis; however, the differences between treatment groups in this sensitivity analysis are similar to those observed in the primary efficacy analysis indicating that the treatment effect is not overly sensitive to the imputation methods used for subjects who drop out. The sponsor also included a "completers response" and a "per-protocol response." These sensitivity analyses were identical to the primary efficacy analysis except that they were conducted in a subset of the subjects. For inclusion in each of these subsets subjects were required to have met certain criteria that were defined in the protocol. The results of both of these analyses were consistent with the primary efficacy results.

Table 13: Sensitivity Analyses of the Primary Efficacy Endpoint for Studies 1056 and 1057

Analyses	Trial 1056			Trial 1057		
	Placebo (N=275)	Belimumab 1mg/kg (N=271)	Belimumab 10 mg/kg (N=273)	Placebo (N=287)	Belimumab 1mg/kg (N=288)	Belimumab 10 mg/kg (N=290)
Unadjusted Response:	93 (34%)	110 (41%)	118 (43%)	125 (44%)	148 (51%)	167 (58%)
Obs. Diff. vs PLO:		7%	9%		8	14
OR (95% CI)[1] vs PLO		1.34 (0.94, 1.89)	1.49 (1.05, 2.11)		1.37 (0.99, 1.90)	1.76 (1.27, 2.45)
P-value		**0.1020**	**0.0239**		**0.0602**	**0.0008**
LOCF Response (adj.):	101 (37%)	118 (445)	132 (48%)	137 (48%)	155 (54%)	182 (63%)
Obs. Diff. vs PLO		7%	12%		6	15
OR (95% CI)[1] vs PLO		1.33 (0.94, 1.89)	1.67 (1.17, 2.36)		1.44 (1.02, 2.03)	1.94 (1.37, 2.76)
P-value		**0.1096**	**0.0043**		**0.0402**	**0.0002**
Completer Response (adj.):	90/193 (47%)	104/205 (51%)	113/200 (57%)	125/225 (56%)	144/236 (61%)	165/240 (69%)
Obs. Diff. vs PLO		4%	10%		5	13
OR (95% CI)[1] vs PLO		1.19 (0.79, 1.80)	1.59 (1.04, 2.41)		1.46 (0.98, 2.18)	1.87 (1.24, 2.81)
P-value		**0.4098**	**0.0308**		**0.0639**	**0.0027**
Per Protocol Response (adj.):	89/261 (34%)	105/258 (41%)	113/263 (43%)	122/278 (44%)	145/278 (52%)	164/281 (58%)
Obs. Diff. vs PLO		7%	9%		8	14
OR (95% CI)[1] vs PLO		1.35 (0.94, 1.94)	1.50 (1.04, 2.14)		1.56 (1.10, 2.22)	1.86 (1.31, 2.65)
P-value		**0.1026**	**0.0281**		**0.0123**	**0.0005**

Obs. Diff. = Observed Difference; PLO = Placebo; adj. = adjusted
[1]Odds Ratio (95% CI) and p-value were from logistic regression for the comparison between each belimumab dose and placebo without adjustment for any covariates
[2]Odds Ratio (95% CI) and p-value were from logistic regression for the comparison between each belimumab dose and placebo with covariates, including baseline SELENA SLEDA ($\leq$ 9 vs $\geq$ 10), baseline proteinuria level (<2 g/24 hr vs $\geq$ 2 g/24 hr equivalent) and race (African descent or indigenous-American descent vs other).
Adapted Sponsor's Table 7-4; p. 89.

Pre-specified subgroup analyses of the primary efficacy endpoint by region, stratification factors, baseline C3, baseline C4, average steroid use and anti-dsDNA were provided by the sponsor. For each subgroup analysis, consistency of the treatment effect across subgroups was evaluated using logistic regression with main effects for treatment, subgroup, and the treatment-by-subgroup interaction. A significant treatment-by-subgroup interaction is evidence that the treatment effect is (either quantitatively or qualitatively) different in the subgroups being considered. The results of these analyses are displayed in Table 14. Statistically significant **qualitative** treatment-by-subgroup interactions were observed in the analyses comparing each belimumab treatment group versus placebo for race (stratification factor) in Study 1056 suggesting that there are differences in the direction of the treatment effect in the racial subgroups. Statistically significant **quantitative** treatment-by-subgroup interactions were observed in the

analyses comparing each belimumab treatment group versus placebo for baseline SELENA SLEDAI score (stratification factor), and in the analyses comparing the belimumab 10 mg/kg versus placebo for baseline C3 and baseline C4 levels in Study 1057. A quantitative interaction refers to cases where there may be a difference in the magnitude of the treatment effect in the subgroups but the direction of the treatment effect does not vary across subgroups.

Table 14: Subgroup Analyses of the Primary Efficacy Endpoint for Trials 1056 and 1057

	Trial 1056			Trial 1057		
	Placebo (N=275)	**Belimumab 1mg/kg (N=271)**	**Belimumab 10 mg/kg (N=273)**	**Placebo (N=287)**	**Belimumab 1mg/kg (N=288)**	**Belimumab 10 mg/kg (N=290)**
Overall Response:	93 (34%)	110 (41%)	118 (43%)	125 (44%)	148 (51%)	167 (58%)
Region:						
USA/Canada	46/145 (32%)	59/155 (38%)	47/136 (35%)	--	--	--
W. Europe/Israel	15/64 (23%)	25/63 (40%)	38/75 (51%)	--	--	--
E. Europe	15 /36 (42%)	11/27 (41%)	16/30 (53%)	12/33 (36%)	21/34 (62%)	23/31 (74%)
Americas (excl. USA/Canada)	17/30 (57%)	15/26 (58%)	17/32 (53%)	71/145 (49%)	85/143 (59%)	85/140 (61%)
Asia	--	--	--	40/103 (39%)	42/106 (40%)	56/115 (49%)
Australia	--	--	--	2/6 (33%)	0/5 (0%)	3/4 (75%)
Interaction P-value[1]	--	**0.5597**	**0.0727**	--	**0.3605**	**0.1800**
Baseline C3						
Normal/High C3	57/159 (36%)	72/171 (42%)	69/158 (44%)	82//155 (53%)	87/140 (62%)	83/143 (58%)
Low C3	36/116 (31%)	38/100 (38%)	49/115 (43%)	43/132 (33%)	61/148 (41%)	84/147 (57%)
Interaction P-value[1]	--	**0.9012**	**0.6295**	--	**0.9836**	**0.0183**
Baseline C4						
Normal/High C4	49/132 (37%)	55/130 (42%)	55/126 (44%)	71/127 (56%)	72/115 (63%)	64/110 (58%)
Low C4	44/143 (31%)	55/141 (39%)	63/147 (43%)	54 (160 (34%)	76/173 (445)	103/180 (57%)
Interaction P-value[1]	--	**0.6795**	**0.4774**	--	**0.6609**	**0.0118**
Baseline Ave. Steroid Use:						
0-≤ 7.5 mg/d	54/149 (36%)	56/141 (40%)	63/153 (41%)	35/95 (37%)	34/84 (41%)	48/86 (56%)
>7.5 mg/d	39/126 (31%)	54/130 (42%)	55/120 (46%)	90/192 (47%)	114/204 (56%)	119/204 (58%)
Interaction P-value[1]	--	**0.3808**	**0.2303**	--	**0.5715**	**0.3947**
Baseline anti-dsDNA						
<30 IU/mL	39/101 (39%)	38/100 (38%)	38/94 (40%)	43/82 (52%)	42/67 (63%)	44/72 (61%)
≥ 30 IU/mL	54/174 (31%)	72/171 (42%)	80/179 (45%)	82/205 (40%)	106/221 (48%)	123/218 (56%)
Interaction P-value[1]	--	**0.1686**	**0.1661**	--	**0.8026**	**0.4166**
Baseline Proteinuria Level (stratification factor):						
< 2g/24 hours equivalent	86/264 (33%)	107/264 (41%)	110/258 (43%)	120/266 (455)	139/262 (53%)	161/271 (59%)
≥ 2 g/24 hours equivalent	7/11 (64%)	3/7 (43%)	8/15 (53%)	5/21 (24%)	9/26 (35%)	6/19 (32%)
Interaction P-value[1]	--	**0.2357**	**0.3037**	--	**0.7590**	**0.7984**
Race (stratification factor):						
AIA	36/74 (49%)	30/74 (41%)	29/72 (40%)	47/100 (47%)	59/106 (56%)	64/103 (62%)
Other	57/201 (28%)	80/197 (41%)	89/201 (44%)	78/187 (42%)	89/182 (49%)	103/187 (55%)
Interaction P-value[1]	--	**0.0265**	**0.0088**	--	**0.8709**	**0.8278**
Baseline SELENA SLEDAI Score (stratification factor):						
≤ 9 points	39/134 (29%)	39/127 (31%)	45/137 (33%)	47/129 (36%)	55/149 (37%)	53/130 (41%)
≥ 10 points	54/141 (38%)	71/144 (49%)	73/136 (54%)	78/158 (49%)	93/139 (67%)	114/160 (71%)
Interaction P-value[1]	--	**0.3031**	**0.2108**	--	**0.0409**	**0.0312**

AIA = African descent or indigenous American descent
[1]For treatment by subgroup interaction effect from logistic regression.
Adapted Sponsor's Table L9-1; Appendix 17.2.6 from the Study Reports for Trials 1056 and 1057.

SLE patients of African American or African heritage have been reported to have more aggressive disease, often leading to worse outcomes. Therefore the significant qualitative treatment-by-race interactions observed for comparison of each belimumab group to

placebo merit special attention. To this end, the Applicant provided post hoc exploratory analysis of treatment effect on race, summarized in Table 15 below. The results of this analysis for Studies 1056 and 1057 suggest that there may be a reversal in the direction of the treatment effect in subjects of African American or African heritage. A similar finding was noted in the Native American subgroup of Study 1056 but not the same subgroup of Study 1057. This illustrates the difficulty of drawing conclusions from these subgroup analyses when subgroups are small.

Table 15: Primary Efficacy Endpoint Results by Racial Subgroups for Studies 1056 and 1057

Race	Trial 1056			Trial 1057		
	Placebo (N=275)	Belimumab 1mg/kg (N=271)	Belimumab 10 mg/kg (N=273)	Placebo (N=287)	Belimumab 1mg/kg (N=288)	Belimumab 10 mg/kg (N=290)
Caucasian	56/188 (30%)	78/192 (41%)	86/189 (46%)	38/82 (46%)	47/76 (62%)	47/71 (66%)
Black /African American or African Heritage	15/39 (39%)	12/40 (30%)	13/39 (33%)	7/11 (64%)	3/8 (38%)	5/11 (46%)
Alaska Native or American Indian	21/36 (58%)	18/33 (55%)	16/34 (47%)	40/89 (45%)	56/98 (57%)	59/92 (64%)
Other	1/12 (8%)	2/6 (33%)	3/11 (27%)	40/105 (38%)	42/106 (40%)	56/116 (48%)
Interaction P-value	--	**0.2009**	**0.0662**	--	**0.2454**	**0.3068**

Adapted Sponsor's Table 7-6; p. 97 and Sponsor's Table 7-6; p. 91 from the Study Reports for Trials 1056 and 1057.

Secondary Endpoints

A number of secondary variables were evaluated in Trials 1056 and 1057 as shown in Table 16 below. No multiplicity correction was planned for the protocols for these studies or implemented here for the secondary endpoints. Due to multiplicity concerns, declaring statistical significance of these secondary endpoints using unadjusted p-values may be inappropriate. The results from the majority of the secondary endpoints evaluated in these trials were unsupportive of the primary analysis. The remaining discussion will highlight major and selected secondary endpoints of interest.

Table 16: Secondary Endpoints Evaluated in Trials 1056 and 1057

Major Secondary Endpoints:

1. Response Rate at Week 76 (Trial C1056 only)
2. Percentage of Subjects with $\geq$ 4 Point Reduction from Baseline in SELENA SLEDAI Score at Week 52
3. Mean Change in SF-36 Health Survey PCS Score at Week 24
4. Mean Change/Percent Change in PGA at Week 24
5. Percentage of Subjects Whose Average Prednisone Dose has been Reduced by $\geq$ 25% from Baseline to $\leq$ 7.5 mg/day During Weeks 40 Through 52

Secondary Endpoints:

Disease Activity:

- Response rate at Weeks 12 and 24
- Time to first response
- Duration of first response
- Percent of patients with $\geq$ 4 point reduction from baseline in SELENA SLEDAI at Weeks 12, 24 and 76.
- Mean change in PGA at week 12 and 52
- Percent change from baseline in SELENA SLEDAI score at Weeks 12, 24, and 52
- Percent of patients with no worsening (increase of <0.30 points from baseline) in PGA at Weeks 12, 24, 52 and 76
- Percent of patients with not new BILAG A organ domain score or new 2 BILAG B organ domain scores compared with baseline at the time of assessment (i.e., at Weeks 12, 24, 52 and 76)
- BILAG response rates at Weeks 12, 24, 52 and 76
- Time to BILAG response
- AUC of the SLENA SLEDAI score over 52 and 76 weeks
- Change in the SLICC/ACR Damage Index at Weeks 52 and 76

- Percent of patients with no new 1A/2B organ domain scores from Week 28 through Week 52
- Percent of patients with no new 1A/2B organ domain scores from Week 52 through Week 76

Flares:

- Time to first SLE flares over 52 and 76 weeks
- Time to first SLE flare after 24 weeks
- Number of flares per subject and the rate of flares over 52and 76 weeks
- Number of flares per subject and the rate of flares from Week 24 to 52 and from Week 24 to 76

Organ Specific Measures:

- Renal flare rate and time to first renal flare
- The rate and duration of renal remission and time to first renal remission
- Percent change in proteinuria

Steroid Reduction:

- Percentage of patients with average steroid dose has been reduced by 25% from baseline to 7.5 mg/day or lower during Weeks 64 through 76
- Percent change from baseline of prednisone dose at Weeks 12, 24, 52 and 76
- Number of days of daily steroid dose $\leq$ 7.5 mg/day and/or reduced by 50% from baseline over time
- Time to reduction of daily prednisone dose $\leq$ 7.5 mg/day and/or reduced by 50% from baseline over 52 weeks and 76 weeks at Weeks 12, 24, 52 and 76
- Percent of patients with daily prednisone dose reduced $\leq$ 7.5 mg/day from > 7.5 mg /day at baseline over time
- Percent of patients with daily steroid dose increased to >7. 5 mg/day from $\leq$ 7.5 mg/day at baseline over time

Biomarkers:

- Percent change from baseline in: total serum Ig, anti-dsDNA, ANA, anti-Sm, aCL, C3, C4, interferon expression signature and T lymphocytes (CD3+/4$^-$ and CD 3$^+$/8$^-$
- Percent change in absolute B cell subsets (CD 20$^+$, CD20$^+$/27$^+$ memory, CD20$^+$/27$^-$ naive, CD20$^+$/69$^+$activated, CD20$^+$/138$^+$ plasmacytoid, CD19$^+$/27^{BRIGHT}/38^{BRIGHT} SLE subset and CD20$^-$/138$^+$ plasma cells) at Weeks 8, 24, 52 and 76

Patient Reported Outcomes:

- Mean change in SF-36 Health Survey PCS score at Weeks 12, 52 and 76
- Mean change in SF-36 Health Survey Score (8 domains) at Weeks 12, 24, 52 and 76
- Mean change in FACIT-Fatigue Scale score at Weeks 12, 24, 52 and 76
- EQ-5D Health Questionnaire at Weeks 12, 24, 52 and 76
- Workplace Productivity Questionnaire at Weeks 12, 24, 52 and 76
- Emergency room visits from Day 0 through Week 12, 24, 52, and 76

Section 8.3 of the Sponsor's Analytical Plans for Protocols 1056 and 1057

Week 76 Response Rate:

If approved, belimumab would be potentially administered as a chronic treatment for SLE. In view of this, durability of treatment effect was evaluated by the group response to treatment by the SRI at Week 76 in Study 1056, which was a prespecified major secondary endpoint. As shown in Table 17, patients in the 1mg/kg and 10 mg/kg belimumab treatment groups had numerically higher response rates than placebo patients at Week 76, but these differences were not significant.

The results from the analyses of the subcomponents of the SRI endpoint at Week 76 for the 1mg/kg belimumab group showed numerical improvement for all subcomponents. The results from the analyses of the three subcomponents of the Week 76 response rate for the 10 mg/kg belimumab group were less robust as a result of the small numerical improvements observed for each subcomponent. Overall, these results differ with those from the Week 52 primary endpoint analyses where the results from the 10 mg/kg belimumab treatment group were more robust than those of the 1 mg/kg belimumab treatment group.

Table 17: Overall Week 76 Responder Rate and Subcomponent Results for Study 1056

	Placebo (N=275)	Belimumab 1mg/kg (N=271)	Belimumab 10 mg/kg (N=272)
Response:	89 (32%)	106 (39%)	105 (39%)
Observed Difference vs Placebo		7%	6%
OR (95% CI)[1] vs Placebo		1.34 (0.94, 1.91)	1.31 (0.92, 1.87)
P-value		**0.1050**	**0.1323**
Subcomponents			
4-Point Reduction in SELENA SLEDAI:	93 (33%)	114 (42%)	113 (41%)
OR (95% CI)[2] vs Placebo		1.42 (1.00, 2.02)	1.39 (0.98, 1.98)
P-value		**0.0486**	**0.0660**
No Worsening in PGA:	160 (58%)	178 (66%)	172 (63%)
OR (95% CI)[3] vs Placebo		1.40 (0.99, 1.99)	1.22 (0.86, 1.72)
P-value		**0.0594**	**0.2703**
No New 1A/2B BILAG Domain Scores	162 (59%)	187 (69%)	173 (63%)
OR (95% CI)[4] vs Placebo		1.58 (1.10, 2.25)	1.20 (0.84, 1.70)
P-value		**0.0123**	**0.3123**

OR=Odds Ratio; CI =Confidence Interval

[1]OR (95% CI) and p-value were from logistic regression for the comparison between each belimumab dose and placebo with covariates including baseline SELENA SLEDAI (≤ 9 vs ≥ 10), baseline proteinuria level (<2 g/24 hour equivalent) and race (AIA vs other)

[2]OR (95% CI) and p-value were from logistic regression for the comparison between each belimumab dose and placebo with covariates as in footnote 1 and baseline PGA

[3]OR (95% CI) and p-value were from logistic regression for the comparison between each belimumab dose and placebo with covariates as in footnote 1 and baseline BILAG domain involvement (at least 1A/2B vs at most 1B)

Table 2.7.3-43 of Sponsor's Summary of Clinical Efficacy

Reduction in Corticosteroids:

In view of the morbidity associated with corticosteroids, reduction in corticosteroid use in patients whose SLE was controlled was included as an important clinically relevant endpoint. This secondary endpoint was defined as the percentage of subjects whose average prednisone dose was reduced by ≥ 25% from baseline to ≤ 7.5 mg/day during Weeks 40 through 52 in subjects who were receiving >7.5 mg/day prednisone at baseline. As noted previously in this review, fewer patients (46%) in Study 1056 were taking >7.5 mg/day of prednisone as compared to patients (69%) in Study 1057 (refer to Table 8). As shown in Table 18, numerically more patients in both belimumab treatment groups were able to reduce their prednisone use by ≥ 25% as compared to placebo in Study 1056. Similarly, in Study 1057, a higher percentage of patients in the 1 mg/kg belimumab group and in the 10 mg/kg belimumab group were able to reduce their prednisone by ≥ 25% as compared to placebo.

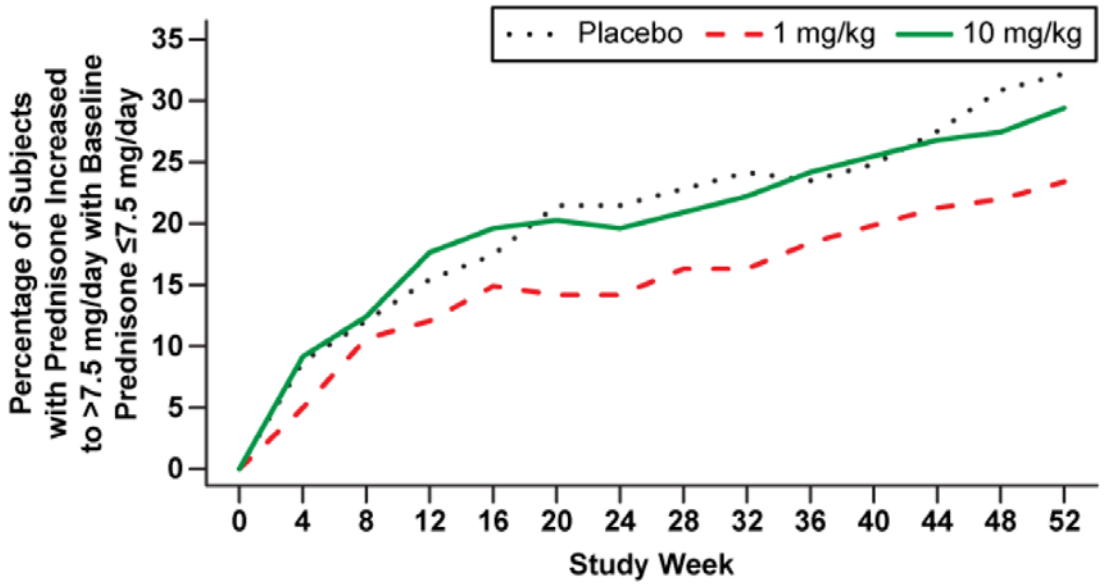
Table 18 Proportion of Patients with Prednisone Reduction by ≥25% from Baseline to ≤7.5 mg/day During Weeks 40 through 52[1] in Studies 1056 and 1057

	Trial 1056			Trial 1057		
	Placebo (N=126)	**Belimumab 1mg/kg (N=130)**	**Belimumab 10 mg/kg (N=120)**	**Placebo (N=192)**	**Belimumab 1mg/kg (N=204)**	**Belimumab 10 mg/kg (N=204)**
Response[2]:	16 (13%)	25 (19%)	20 (17%)	23 (12%)	42 (21%)	36 (19%)
Observed Difference vs Placebo		7%	4%		9%	7%
OR (95% CI)[3] vs Placebo		1.57 (0.78, 3.14)	1.26 (0.61, 2.60)		1.89 (1.08, 3.31)	1.75 (0.99, 3.08)
P-value[3]		**0.2034**	**0.5323**		**0.0252**	**0.0526**

[1]Includes only subjects with baseline prednisone > 7.5 mg/day
[2]Any subject who withdrew from the study prior to the Day 364 (Week 52) visit, missed the Day 364 (Week 52) visit (± 28 day window allowed) and/or received a protocol-prohibited medication or a dose of allowable (but protocol-restricted) medication that resulted in treatment failure designation prior to the Day 364 (Week 52) visit was considered a treatment failure for prednisone reduction.
[3]OR (95% CI) and p-value were from logistic regression for the comparison between each belimumab dose and placebo with covariates, including baseline prednisone level and stratification factors.
Adapted Sponsor's Table 7-24; p. 135 and Sponsor's Table 7-15; p.114.

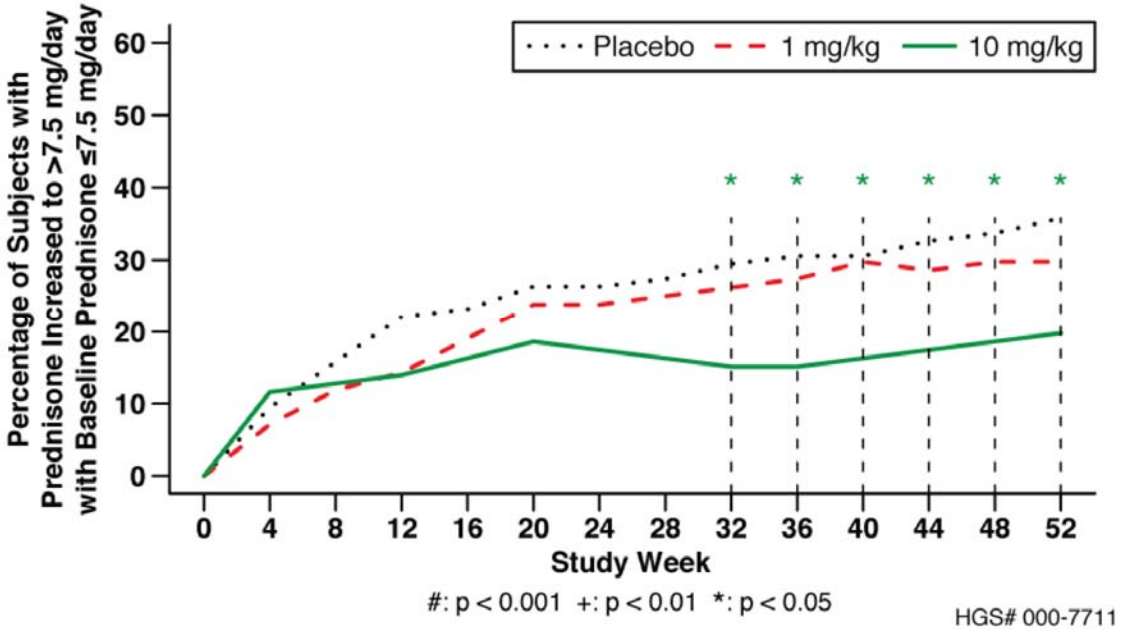
Subjects in these trials were also evaluated for increases in concomitant corticosteroids. The following Figures 1 and 2 depict the percentage of subjects whose daily prednisone dose was increased to >7.5 mg/day from ≤ 7.5 mg/day at baseline over time in Studies 1056 and 1057, respectively. Over the course of Study 1056, a numerically smaller percentage of subjects in the belimumab 1 mg/kg group had their daily prednisone dose increased to > 7.5 mg/day as compared to placebo while the percentage of patients in the 10 mg/kg belimumab group whose daily prednisone dose was increased to > 7.5 mg/day was similar to that of the placebo group. In contrast, a smaller percentage of patients in the 10 mg/kg belimumab group had their daily prednisone dose increased to >7.5 mg/day as compared to the placebo group in Study 1057. The percent difference between the 10 mg/kg belimumab and placebo treatment groups was numerically different starting at Week 32 and appeared to sustain through Week 52 for this trial. The percentage of patients in the 1 mg/day group whose daily prednisone dose was increased to >7.5 mg/day was numerically smaller than the placebo group at all timepoints but the difference did not approach statistical significance. Although belimumab treatment appeared to be associated with a lower proportion of patients requiring a prednisone increase compared to placebo treatment in both studies, the inconsistency with respect to dose is difficult to explain.

Figure 1: Percentage of Subjects Requiring an INCREASE in Daily Prednisone to >7.5 mg/day from <7.5 mg/day at Baseline (Imputation: Dropout=Failure) in Study 1056



Sponsor's Fig. 7-14; p. 140 of the Study Report for Study 1056

Figure 2: Percentage of Subjects Requiring an INCREASE in Daily Prednisone to >7.5 mg/day from <7.5 mg/day at Baseline (Imputation: Dropout=Failure) in Study 1057



Sponsor's Fig. 7-13B; p. 119 of Study Report for Study 1057

Flares:

SLE flares were defined in 2 ways:
1) Modified SELENA SLEDAI SLE Flare Index (SFI), where the modification excludes severe flares that are triggered *only* by an increase of SELENA SLEDAI score to > 12

(i.e., at least one of the other severe flare criterion on the SFI must be present irrespective of the SELENA SLEDAI score) [see Table 19];
2) New BILAG A organ domain score or 2 new BILAG B organ domain scores compared with baseline.

Table 19: SELENA Trial Definition of SLE Flares

'Mild/moderate flare'	*'Severe flare'*
• a change in SLEDAI ≥ 3 points, or • new/worse skin, stomatitis, serositis, arthritis, fever, or • increased prednisone < 0.5 mg/kg/d, or • added NSAID/Plaquenil, or • ≥ 1.0 increase in a physician's global assessment (0–3 scale)	• change in SLEDAI > 12, or • new/worse CNS-SLE, vasculitis, nephritis, myositis, Plt < 60,000 hemolytic anemia with Hb < 7 mg/dl, requiring doubling or > 0.5 mg/kg/d prednisone, or • hospitalization for SLE, or • prednisone > 0.5 mg/kg/d, or • new immunosuppressive, or • increased physician's global assessment to > 2.5

Source: Petri et al. Lupus 1999; 8:685-91

Table 20 displays the results from the flare analyses assessed by the modified SLE Flare Index. In Study 1056, the median time to first flare was similar for all three treatment groups with durations ranging from 82-85 days. In contrast, in Study 1057, the median time to flare for both the 1mg/kg (126 days) and 10 mg/kg (119 days) belimumab groups was longer as compared to placebo (84 days). In Study 1056, the risk for having a severe disease flare over 52 weeks was reduced only in the 1 mg/kg belimumab group, whereas in Study 1057 the risk was reduced only in the 10 mg/kg belimumab group. The results suggest there may be a treatment benefit of belimumab with respect to flares.

Table 20: SLE Flare Results over 52 Weeks in Studies 1056 and 1057

	Trial 1056			**Trial 1057**		
	Placebo (N=275)	**Belimumab 1mg/kg (N=271)**	**Belimumab 10 mg/kg (N=273)**	**Placebo (N=287)**	**Belimumab 1mg/kg (N=288)**	**Belimumab 10 mg/kg (N=290)**
Any Flare[1]:						
n (%)[2]	228 (83%)	214 (79%)	215 (79%)	230 (80%)	203 (71%)	205 (71%)
Median Time to 1st Flare in Days (Min, Max)[3]	82 (34, 195)	85 (41, 249)	84 (35, 228)	84 (1, 368)	126 (5, 375)	119 (1, 367)
Hazard Ratio (95% CI) vs PLO[4]		0.89 (0.74, 1.08)	0.93 (0.78, 1.13)	-	0.75 (0.62,0.90)	0.76 (0.63, 0.91)
P-value[4]		**0.2324**	**0.4796**	-	**0.0026**	**0.0036**
Severe Flare[1]:						
n (%)[2]	67 (24%)	44 (16%)	48 (18%)	66 (23%)	51 (18%)	40 (14%)
Median Time to 1st Flare in Days (Min, Max)[3]	- (1, 370)	- (3, 322)	- (10, 361)	-(5, 371)	- (5, 364)	- (1, 366)
Hazard Ratio (95% CI) vs PLO[4]		0.64 (0.44, 0.94)	0.72 (0.50, 1.05)	-	0.76 (0.52, 1.09)	0.57 (0.39, 0.85)
P-value[4]		**0.0230**	**0.0867**	-	**0.1342**	**0.0055**
Flare per Subject-Year[5]	n=272	n=267	n= 270	n=284	n=286	n=287
Mean ± SE	3.81 ± 0.18	3.33 ± 0.18	3.42 ± 0.19	3.22 ± 0.17	2.50 ± 0.17	2.37 ± 0.16
P-value[6]		**0.0632**	**0.1276**		**0.0012**	**0.0002**
Severe Flares per Subject-Year[5]						
Mean ± SE	1.11 ± 0.14	0.93 ± 0.15	1.00 ± 0.15	0.92 ± 0.12	0.80 ± 0.12	0.59 ± 0.10
P-value[6]		**0.3680**	**0.5775**		**0.3544**	**0.0381**

[1]Censored at last available visit. For 9 subjects who died, censored at death if no flares indicated before death. Any increase of ≥ 3 points on SLEDAI score resulted in a mild/moderate flare.
[2]Number (%) of subjects with at least 1 flare over 52 weeks.
[3]One or more of Q1 or/and Q3 values are not available, observed (MIN, Max) presented. The median time to flare can not be observed when less than 50% of subjects experience a flare.
[4]From Cox proportional hazards model for the comparison between each belimumab dose and placebo, adjusted for baseline stratification factors.

[5]Includes subjects who did not dropout or had medication failures before Day 28; 0 flares assigned for missing visits before exit/treatment failure date.
[6]From ANCOVA model for the comparison between each belimumab dose and placebo, adjusted for baseline stratification factors.
Adapted Sponsor's Table 7-9; p. 99. Adapted Sponsor's Table 7-18; p. 120.

The occurrence of flares was also assessed from Weeks 24 to 52 following the implementation of background medication restrictions (Table 21 below). Decreases in the risk for experiencing a disease flare during this time period were observed in both belimumab groups in Study 1056 and Study 1057.

Table 21: SLE Flare Results from Week 24 to Week 52 in Studies 1056 and 1057

	Trial 1056			Trial 1057		
	Placebo (N=238)	**Belimumab 1mg/kg (N=245)**	**Belimumab 10 mg/kg (N=235)**	**Placebo (N=254)**	**Belimumab 1mg/kg (N=263)**	**Belimumab 10 mg/kg (N=271)**
Any Flare[1]:						
No. of Subjects[2]	176 (74%)	161 (66%)	150 (64%)	161 (63%)	117 (45%)	141 952%)
Median Time to 1st Flare in Days (Min, Max)[3]	76 (1, 218)	105 (1, 201)	98 (1, 204)	112 (3, 201)	207 (2, 207)	182 (2, 203)
Hazard Ratio (95% CI) vs PLO[4]		0.81 (0.66, 1.10)	0.78 (0.62, 0.97)		0.58(0.46, 0.74)	0.71 (0.56, 0.89)
P-value[4]		**0.0583**	**0.0226**		**<0.0001**	**0.0027**
Severe Flare:						
No. of Subjects[2]	43 (18%)	25 (10%)	28 (12%)	28 (11%)	21 (8%)	21 (8%)
Median Time to 1st Flare in Days (Min, Max)[3]	- (1, 199)	- (1, 154)	-(6, 193)	- (3, 206)	- (2, 196)	- (7, 200)
Hazard Ratio (95% CI) vs PLO[4]		0.55 (0.33, 0.90)	0.66 (0.41, 1.06)		0.72 (0.41, 1.26)	0.70 (0.40, 1.23)
P-value[4]		**0.0167**	**0.0843**		**0.2476**	**0.2167**
Flare per Subject-Year[5]	n= 227	n=236	n=229	n=246	n=257	N=264
Mean ± SE	3.89 ± 0.26	3.06 ± 0.21	2.95 ± 0.22	3.00 ± 0.24	1.92 ± 0.18	1.90 ± 0.15
P-value[6]		**0.0091**	**0.0045**		**<0.0001**	**<0.0001**
Severe Flares per Subject-Year[5]						
Mean ± SE	1.09 ± 0.20	0.79 ± 0.17	0.82 ± 0.16	0.82 ± 0.18	0.58 ± 0.14	0.45 ± 0.10
P-value[6]		**0.1898**	**0.3106**		**0.1851**	**0.0714**

[1]Censored at last available visit by Week 52 after Week 24. For 9 subjects who died, censored at death if no flares indicated after Week 24 and before death. Any increase of ≥ 3 points on SLEDAI score resulted in a mild/moderate flare.
[2]Number (%) of subjects with at least 1 flare between Week 24 and Week 52 among subjects with at least 1 visit after Week 24.
[3]One or more of Q1 or/and Q3 values are not available, observed (Min, Max) presented. The median time to flare can not be observed when less than 50% of subjects experience a flare.
[4]From Cox proportional hazards model for the comparison between each belimumab dose and placebo, adjusted for baseline stratification factors.
[5]Includes subjects who did not dropout or had medication failures within 28 days post Week 24; 0 flares assigned for missing visits before exit/treatment failure date.
[6]From ANCOVA model for the comparison between each belimumab dose and placebo, adjusted for baseline stratification factors.
Adapted Sponsor's Table 7-19; p. 122. Adapted Sponsor's Table 7-10; p. 101.

No reduction in risk for developing a BILAG 1A/2B organ domain flare over 52 weeks was observed in either of the belimumab treatment groups in Study 1056 as displayed in the following Table 22. Flares per subject years as assessed by the BILAG were also comparable for the 3 treatment groups and ranged from 1.32 to 1.45 flares/year in this trial. However in Study 1057, subjects in the 10 mg/kg belimumab treatment group had a reduction in flares per subject years as well as a reduction in risk for developing a BILAG 1A/2B organ flare as compared to placebo.

Table 22: BILAG Flares over 52 Weeks in Studies 1056 and 1057

	Trial 1056			Trial 1057		
	Placebo (N=287)	**Belimumab 1mg/kg (N=288)**	**Belimumab 10 mg/kg (N=290)**	**Placebo (N=254)**	**Belimumab 1mg/kg (N=263)**	**Belimumab 10 mg/kg (N=271)**
Time to 1st BILAG 1A/2B Flare[1]:						
n (%)[2]	92 (34%)	75 (28%)	86 (32%)	86 (30%)	77 (27%)	54 (19%)
Median Time to 1st Flare in Days (Min, Max)[3]	385 (27, 385)	- (15, 335)	- (26, 364)	- (24, 367)	- (27, 368)	- (1, 366)
Hazard Ratio (95% CI) vs PLO[4]		0.78 (0.58, 1.06)	0.93 (0.69, 1.24)		0.89 (0.66, 1.22)	0.58 (0.41, 0.81)
P-value[4]		**0.1191**	**0.6135**		**0.4804**	**0.0016**
Time to 1st BILAG 1A Flare (post hoc analysis):						
No. of Subjects[2]	72 (26%)	52 (19%)	62 (23%)	58 (20%)	54 (19%)	29 (10%)
Median Time to 1st Flare in Days (Min, Max)[3]	385 (27, 385)	- (15, 315)	- (27, 364)	- (24, 367)	- (27, 351)	- (1, 366)
Hazard Ratio (95% CI) vs PLO[4]		0.71 (0.50, 1.01)	0.88 (0.63, 1.24)		0.88 (0.61, 1.28)	0.45 (0.28, 0.70)
P-value[4]		**0.0593**	**0.4744**		**0.4997**	**0.0004**
Flare per Subject-Year[5]	n=272	n=267	N=270	n=284	n=286	n=287
Mean ± SE	1.5 ± 0.16	1.3 ± 0.17	1.39 ± 0.16	1.21 ± 0.14	1.04 ± 0.14	0.75 ± 0.11
P-value[6]		**0.4616**	**0.5828**		**0.3225**	**0.0104**

[1]Censored at last available visit by Week 52 visit. For 9 subjects who died, censored at death if no flares indicated before death.
[2]Number (%) of subjects with at least 1 flare over 52 weeks.
[3]One or more of Q1 or/and Q3 values are not available, observed (Min, Max) presented. The median time to flare results should be interpreted with caution when a majority of subjects did not experience a flare since sample sizes used to estimate the median may be small due to censoring
[4]From Cox proportional hazards model for the comparison between each belimumab dose and placebo, adjusted for baseline BILAG domain involvement (at least 1A/2B vs at most 1B) and stratification factors.
[5]Includes subjects who did not dropout or had medication failures before Day 28; 0 flares assigned for missing visits before exit/treatment failure date.
[6]From ANCOVA model for the comparison between each belimumab dose and placebo, adjusted for baseline BILAG domain involvement (at least 1A/2B vs at most 1B) and stratification factors.
Adapted Sponsor's Table 7-21; p. 130. Adapted Sponsor's Table 7-12; p. 110.

The occurrence of BILAG flares was also assessed from Weeks 24 to 52. Decreases in the risk for experiencing a disease flare during this time period were observed in both belimumab groups in Study 1056 and in Study 1057.

Table 23: BILAG Flares from Week 24 to Week 52 in Studies 1056 and 1057

	Trial 1056			Trial 1057		
	Placebo (N=287)	Belimumab 1mg/kg (N=288)	Belimumab 10 mg/kg (N=290)	Placebo (N=254)	Belimumab 1mg/kg (N=263)	Belimumab 10 mg/kg (N=271)
Time to 1st BILAG 1A/2B Flare[1]:						
n (%)[2]	65 (27%)	47 (19%)	47 (20%)	49 (19%)	38 (14%)	32 (12%)
Median Time to 1st Flare in Days (Min, Max)[3]	218 (7, 218)	- (1, 167)	- (6, 202)	- (7, 199)	- (2, 200)	- (7, 200)
Hazard Ratio (95% CI) vs PLO[4]		0.67 (0.46, 0.98)	0.70 (0.48, 1.02)		0.74 (0.48, 1.13)	0.58 (0.37, 0.91)
P-value[4]		0.0394	0.0609		0.1566	0.0185
Flare per Subject-Year[5]	n=227	n=236	n=229	n=246	n=257	n=264
Mean ± SE	1.5 ± 0.21	1.3 ± 0.22	1.2 ±0.20	1.29 ± 0.21	0.88 ± 0.15	0.64 ± 0.11
P-value[6]		0.4043	0.3152		0.0611	0.0041

[1]Censored at last available visit. For 9 subjects who died, censored at death if no flares indicated before death.
[2]Number (%) of subjects with at least 1 flare over 52 weeks.
[3]One or more of Q1 or/and Q3 values are not available, observed (MIN, Max) presented. The median time to flare can not be observed when less than 50% of subjects experience a flare.
[4]From Cox proportional hazards model for the comparison between each belimumab dose and placebo, adjusted for baseline BILAG domain involvement (at least 1A/2B vs at most 1B) and stratification factors.
[5]Includes subjects who did not dropout or had medication failures before Day 28; 0 flares assigned for missing visits before exit/treatment failure date.
[6]From ANCOVA model for the comparison between each belimumab dose and placebo, adjusted for baseline BILAG domain involvement (at least 1A/2B vs at most 1B) and stratification factors.
Adapted Sponsor's Table 7-22; p. 132. Adapted Sponsor's Table 7-13; p. 111.

Physician's Global Assessment (PGA):

Table 24 displays the results of another prespecified major secondary endpoint, the PGA percent change and change from baseline at Week 24 for both trials. In Study 1056, the improvements in both the mean percent change and mean change from baseline in PGA scores were comparable for all three treatment groups. In contrast, both belimumab treatment groups had greater improvements in the mean percent change in PGA scores and mean change in PGA score at Week 24 as compared to placebo in Study 1057. These results are supportive of those from the Week 52 primary endpoint for Study 1057.

Table 24: Percent Change and Absolute Change in PGA from Baseline to Week 24 for Studies 1056 and 1057

	Trial 1056			Trial 1057		
	Placebo (N=275)	Belimumab 1mg/kg (N=271)	Belimumab 10 mg/kg (N=273)	Placebo (N=287)	Belimumab 1mg/kg (N=271)	Belimumab 10 mg/kg (N=273)
Percent Change:						
Mean ± SE	-26.18 ± 4.21	-28.1 ± 3.6	-27.57 ± 3.37	-22.44 ± 2.64	-29.50 ± 2.17	-36.75 ± 2.39
LS Mean ± SE[1]	-0.49 ± 0.05	-0.49 ± 0.06	-0.48 ± 0.05			
P-value[1]		**0.5149**	**0.4682**		**0.0342**	**<0.0001**
Change:						
Mean ± SE	-0.49 ± 0.04	-0.47 ± 0.04	-0.44 ± 0.03	-0.39 ± 0.03	-0.44 ± 0.03	-0.54 ± 0.03
LS Mean ± SE[1]	-28.16 ± 6.17	-31.52 ± 6.30	-31.90 ± 6.04			
P-value[1]		**0.9545**	**0.7987**		**0.2712**	**0.0003**

[1]All statistics, including the difference in LS (least square) means, were from ANCOVA model for the comparison between each belimumab dose and placebo, adjusted for the baseline PGA score, baseline SELENA SLEDAI score (≤ 9 vs ≥ 10), baseline proteinuria level (< 2 g/24 hr equivalent) and race (AIA vs other).
Adapted Sponsor's Table 7-20; p. 125. Adapted Sponsor's Table 7-11; p. 103.

Improvement and Worsening by Organ Domains:

Although the SLEDAI is not grouped by organ systems, in order to facilitate analysis of treatment effect by systems, the Applicant grouped individual items into organ systems similar to BILAG organ domains for exploratory analyses. (Improvement and worsening by actual BILAG organ domains is summarized in Tables 25 and 26 below). With the exception of the "Immunology" domain, which consists of anti-dsDNA and complement laboratory tests, there was no consistent pattern of improvement and worsening that would support a treatment benefit in favor of belimumab. For most organ systems (notable exceptions—cardiorespiratory in Study 1056, hematological and fever in Study 1057) there was at least a numeric trend suggestive of an improvement with belimumab.

Table 25: Improvement by SELENA-SLEDAI Organ Systems

SELENA-SLEDAI Improvement by Organ Systems, from Baseline to Week 52						
	Study 1056			Study 1057		
Enrolled, n	Placebo n = 275	1 mg/kg n = 271	10 mg/kg n = 273	Placebo n = 287	1 mg/kg n = 288	10 mg/kg n = 290
Mucocutaneous						
Baseline involvement	n = 233	n = 228	n = 209	n = 236	n = 228	n = 245
Number (%) Improved at Week 52	96 (41)	100 (44)	101 (48)	115 (49)	133 (58)	148 (60)
P-value		0.5639	0.1328		**0.0384**	**0.0103**
Immunology						
Baseline involvement	n = 205	n = 195	n = 207	n = 234	n = 250	n = 248
Number (%) Improved at Week 52	20 (10)	43 (22)	55 (27)	24 (10)	47 (19)	69 (28)
P-value		**0.0010**	**<0.0001**		**0.0088**	**<0.0001**
Musculoskeletal						
Baseline involvement	n = 207	n = 193	n = 194	n = 165	n = 169	n = 174
Number (%) Improved at Week 52	88 (43)	94 (49)	92 (47)	95 (58)	117 (69)	116 (67)
P-value		0.2142	0.3234		**0.0275**	0.0850
CNS						
Baseline involvement	n = 6	n = 9	n = 13	n = 5	n = 6	n = 6
Number (%) Improved at Week 52	0	5 (56)	9 (69)	1 (20)	4 (67)	3 (50)
P-value		**0.0440**	**0.0108**		0.2424	0.5455
CardioRespiratory						
Baseline involvement	n = 18	n = 26	n = 27	n = 14	n = 10	n = 10
Number (%) Improved at Week 52	11 (61)	12 (46)	13 (48)	7 (50)	5 (50)	7 (70)
P-value		0.3308	0.3947		1.0000	0.3318
Vascular						
Baseline involvement	n = 17	n = 20	n = 10	n = 20	n = 16	n = 28
Number (%) Improved at Week 52	6 (35)	8 (40)	6 (60)	9 (45)	11 (69)	22 (79)
P-value		0.7688	0.2180		0.1589	0.0198
Hematological and Fever						
Baseline involvement	n = 28	n = 34	n = 33	n = 20	n = 23	n = 21
Number (%) Improved at Week 52	9 (32)	19 (56)	10 (30)	13 (65)	10 (43)	8 (38)
P-value		0.0645	0.8772		0.1617	0.0890
Renal						
Baseline involvement	n = 31	n = 29	n = 33	n = 61	n = 61	n = 52
Number (%) Improved at Week 52	12 (39)	13 (45)	17 (52)	27 (44)	30 (49)	25 (48)
P-value		0.6312	0.3051		0.5863	0.6852

Source: Tables TA46.1, TA46.2, TA46.3, TA46.4, TA46.5, TA46.6, TA46.7, TA46.8
P-values were from logistic regression for the comparison between each belimumab dose and placebo.
CNS items include: cranial nerve disorder, lupus headache, organic brain syndrome, psychosis, seizure, visual disturbance
Cardiorespiratory items include: pericarditis and pleurisy
Vascular items include: CVA and vasculitis
Musculoskeletal items include: arthritis and myositis
Immunology items include: increased DNA binding and low complement
Hematology & Fever items include: leukopenia, thrombocytopenia, and fever
Renal items include: hematuria, proteinuria, pyuria, and urinary casts
Mucocutaneous items include: alopecia, mucosal ulcers, and rash

Table 26: Worsening (New Involvement) by SELENA-SLEDAI Organ Domains

SELENA-SLEDAI New Involvement by Organ Systems, from Baseline to Week 52						
	Study 1056			Study 1057		
Enrolled, n	Placebo n = 275	1 mg/kg n = 271	10 mg/kg n = 273	Placebo n = 287	1 mg/kg n = 288	10 mg/kg n = 290
Mucocutaneous						
# without baseline involvement	n = 42	n = 43	n = 64	n = 51	n = 60	n = 45
Number (%) Involved at Week 52	9 (21.4)	7 (16.3)	9 (14.1)	3 (5.9)	7 (11.7)	5 (11.1)
P-value		0.5444	0.326		0.2976	0.3624
Immunology						
# without baseline involvement	n = 70	n = 76	n = 66	n = 53	n = 38	n = 42
Number (%) Involved at Week 52	15 (21.4)	7 (9.2)	4 (6.1)	8 (15.1)	10 (26.3)	4 (9.5)
P-value		**0.0445**	**0.015**		0.1897	0.4207
Musculoskeletal						
# without baseline involvement	n = 68	n = 78	n = 79	n = 122	n = 119	n = 116
Number (%) Involved at Week 52	7 (10.3)	8 (10.3)	6 (7.6)	6 (4.9)	4 (3.4)	2 (1.7)
P-value		0.9940	0.5670		0.5469	0.1911
CNS						
# without baseline involvement	n = 269	n = 262	n = 260	n = 282	n = 282	n = 284
Number (%) Involved at Week 52	2 (0.7)	1 (0.4)	2 (0.8)	0	2 (0.7)	0
P-value		1.0000	1.0000		0.4991	
CardioRespiratory						
# without baseline involvement	n = 257	n = 245	n = 246	n = 273	n = 278	n = 280
Number (%) Involved at Week 52	9 (3.5)	4 (1.6)	4 (1.6)	1 (0.4)	0	0
P-value		0.1813	0.1789		0.4955	0.4937
Vascular						
# without baseline involvement	n = 258	n = 251	n = 263	n = 267	n = 272	n = 262
Number (%) Involved at Week 52	1 (0.4)	1 (0.4)	2 (0.8)	1 (0.4)	1 (0.4)	1 (0.4)
P-value		1.0000	1.0000		1.0000	1.0000
Hematological and Fever						
# without baseline involvement	n = 247	n = 237	n = 240	n = 267	n = 265	n = 269
Number (%) Involved at Week 52	17 (6.9)	11 (4.6)	10 (4.2)	19 (7.1)	15 (5.7)	13 (4.8)
P-value		0.2940	0.1948		0.4931	0.2673
Renal						
# without baseline involvement	n = 244	n = 242	n = 240	n = 226	n = 227	n = 238
Number (%) Involved at Week 52	18 (7.4)	8 (3.3)	14 (5.8)	22 (9.7)	14 (6.2)	17 (7.1)
P-value		0.0519	0.4953		0.1638	0.3163

Source: Tables TA47.1, TA47.2, TA47.3, TA47.4, TA47.5, TA47.6, TA47.7, TA47.8
P-values were from logistic regression for the comparison between each belimumab dose and placebo.
Denominator is subjects with no involvement in the given organ item at baseline
CNS items include: cranial nerve disorder, lupus headache, organic brain syndrome, psychosis, seizure, visual disturbance
Cardiorespiratory items include: pericarditis and pleurisy
Vascular items include: CVA and vasculitis
Musculoskeletal items include: arthritis and myositis
Immunology items include: increased DNA binding and low complement
Hematology & Fever items include: leukopenia, thrombocytopenia, and fever
Renal items include: hematuria, proteinuria, pyuria, and urinary casts
Mucocutaneous items include: alopecia, mucosal ulcers, and rash

With respect to new organ involvement, as summarized in Table 26 above, for most organ groupings there was a trend toward more new organ involvement in the placebo group, particularly in Study 1056. There was again some inconsistency, with more new mucocutaneous involvement occurring in the belimumab treatment groups of Study 1057.

When using BILAG organ domains to assess improvement or worsening, results are similar in that there appears to be a numeric trend in favor of belimumab in most organ domains, with the exception of the cardiorespiratory subgroup in Study 1057 and the vasculitis subgroup of Study 1056 (see Table 27 below).

Table 27: BILAG Organ Domain Improvement from Baseline to Week 52

BILAG Organ Domain Improvement from Baseline to Week 52						
	Study 1056			Study 1057		
	Placebo n = 275	1 mg/kg n = 271	10 mg/kg n = 273	Placebo n = 287	1 mg/kg n = 288	10 mg/kg n = 290
BILAG: General						
Baseline Domain Score A or B	n = 38	n = 30	n = 38	n = 28	n = 23	n = 26
Number of pts with A	2	1	0	3	0	3
Number of pts with B	36	29	38	25	23	23
Number (%) improved at Wk 52	19 (50)	16 (53)	21 (55)	18 (64)	17 (74)	19 (73)
p-value of difference		0.7848	0.6458		0.459	0.4861
BILAG: Mucocutaneous						
Baseline Domain Score A or B	n = 178	n = 159	n = 141	n = 172	n = 167	n = 174
Number of pts with A	15	16	12	9	12	10
Number of pts with B	163	143	129	163	155	164
Number (%) improved at Wk 52	65 (37)	67 (42)	56 (40)	72 (42)	89 (53)	94 (54)
p-value of difference		0.2913	0.5588		**0.0349**	**0.0234**
BILAG: Musculoskeletal						
Baseline Domain Score A or B	n = 195	n = 177	n = 179	n = 147	n = 150	n = 160
Number of pts with A	14	11	10	33	33	25
Number of pts with B	181	166	169	114	117	135
Number (%) improved at Wk 52	88 (45)	92 (52)	94 (53)	83 (56)	108 (72)	110 (69)
p-value of difference		0.1866	0.1533		**0.0051**	**0.0259**
BILAG: Neurological						
Baseline Domain Score A or B	total of 20 subjects			total of 1 subject		
Number of pts with A	not reported			not reported		
Number of pts with B	not reported			not reported		
Number (%) improved at Wk 52	not reported			not reported		
p-value of difference	not reported			not reported		
BILAG: CardioRespiratory						
Baseline Domain Score A or B	n = 9	n = 13	n = 15	n = 12	n = 6	n = 6
Number of pts with A	2	2	1	2	3	1
Number of pts with B	7	11	14	10	3	5
Number (%) improved at Wk 52	5 (56)	8 (62)	11 (73)	8 (67)	4 (67)	3 (50)
p-value of difference		1.0000	0.4120		1.0000	0.6267
BILAG: Vasculitis						
Baseline Domain Score A or B	n = 30	n = 23	n = 18	n = 22	n = 25	n = 33
Number of pts with A	7	9	3	7	7	16
Number of pts with B	23	14	15	15	18	17
Number (%) improved at Wk 52	15 (50)	13 (57)	7 (39)	10 (45)	19 (76)	29 (88)
p-value of difference		0.6371	0.4532		**0.0304**	**0.0006**
BILAG: Renal						
Baseline Domain Score A or B	n = 21	n = 14	n = 24	n = 38	n = 48	n = 34
Number of pts with A	0	1	1	1	5	2
Number of pts with B	21	13	23	37	43	32
Number (%) improved at Wk 52	9 (43)	10 (71)	12 (50)	22 (58)	23 (48)	19 (56)
p-value of difference		0.0926	0.6316		0.3570	0.8633
BILAG: Hematology						
Baseline Domain Score A or B	n = 36	n = 40	n = 35	n = 52	n = 56	n = 53
Number of pts with A	0	0	1	1	2	3
Number of pts with B	36	40	34	51	54	50
Number (%) improved at Wk 52	9 (25)	16 (40)	11 (31)	19 (34)	19 (36)	32 (36)
p-value of difference		0.1623	0.5469		0.2722	0.3804

Source: Tables T38, T40, T42, T44, T46, T48, T50, T52 from Summary of Clinical Efficacy Appendices
Dropouts/Medication failure = no improvement
P-values were from likelihood ratio test or Fisher's exact test for individual studies

However, the proportion of patients experiencing worsening in BILAG organ domain scores was similar among all three treatment groups of each study (see Table 28, below).

Table 28: Worsening in BILAG from Baseline to Week 52, by Organ Domain

	Study 1056			Study 1057		
	Placebo	1 mg/kg	10 mg/kg	Placebo	1 mg/kg	10 mg/kg
Enrolled, n	n = 275	n = 271	n = 273	n = 287	n = 288	n = 290
BILAG: General						
Baseline Domain Score	n = 273	n = 270	n = 273	n = 284	n = 288	n = 287
Number of pts with B	36 (13)	29 (11)	38 (14)	25 (9)	23 (8)	23 (8)
Number of pts with C	164 (60)	176 (65)	162 (59)	106 (37)	99 (34)	94 (33)
Number of pts with D	11 (4)	7 (3)	4 (1)	11 (4)	11 (4)	13 (5)
Number of pts with E	62 (23)	58 (21)	69 (25)	142 (50)	155 (54)	157 (55)
Number (%) worsened at Wk 52	9 (3)	10 (4)	8 (3)	9 (3)	6 (2)	11 (4)
p-value of difference		0.7963	0.8053		0.4151	0.6659
BILAG: Mucocutaneous						
Baseline Domain Score	n = 260	n = 255	n = 261	n = 278	n = 276	n = 280
Number of pts with B	163 (63)	143 (56)	129 (49)	163 (59)	155 (56)	164 (59)
Number of pts with C	67 (26)	82 (32)	85 (33)	84 (30)	75 (27)	81 (29)
Number of pts with D	7 (3)	3 (1)	7 (3)	2 (1)	4 (1)	5 (2)
Number of pts with E	23 (9)	27 (11)	40 (15)	29 (10)	42 (15)	30 (11)
Number (%) worsened at Wk 52	10 (4)	11 (4)	15 (6)	14 (5)	12 (4)	14 (5)
p-value of difference		0.7885	0.3085		0.7016	0.9845
BILAG: Musculoskeletal						
Baseline Domain Score	n = 261	n = 260	n = 263	n = 254	n = 255	n = 265
Number of pts with B	181 (69)	166 (64)	169 (64)	114 (45)	117 (46)	135 (51)
Number of pts with C	50 (19)	66 (25)	63 (24)	68 (27)	79 (31)	65 (25)
Number of pts with D	5 (2)	5 (2)	7 (3)	3 (1)	3 (1)	5 (2)
Number of pts with E	25 (10)	23 (9)	24 (9)	69 (27)	56 (22)	60 (23)
Number (%) worsened at Wk 52	17 (7)	11 (4)	17 (6)	9 (4)	3 (1)	26 (5)
p-value of difference		0.2462	0.9816		0.9932	0.0622
BILAG: Neurological						
Baseline Domain Score	n = 275	n = 268	n = 272	n = 287	n = 288	n = 290
Number of pts with B	6 (2)	4 (1)	6 (2)	0	1 (0.3)	0
Number of pts with C	36 (13)	40 (15)	55 (20)	20 (7)	26 (9)	22 (8)
Number of pts with D	7 (3)	5 (2)	2 (1)	5 (2)	2 (1)	3 (1)
Number of pts with E	226 (82)	219 (82)	209 (77)	262 (91)	259 (90)	265 (91)
Number (%) worsened at Wk 52	3 (1)	2 (1)	5 (2)	1 (0.3)	1 (0.3)	1 (0.3)
p-value of difference		1.0000	0.5026		1.0000	1.0000
BILAG: CardioRespiratory						
Baseline Domain Score	n = 273	n = 269	n = 272	n = 285	n = 285	n = 289
Number of pts with B	7 (3)	11 (4)	14 (5)	10 (4)	3 (1)	5 (2)
Number of pts with C	51 (19)	48 (18)	47 (17)	23 (8)	21 (7)	25 (9)
Number of pts with D	9 (3)	8 (3)	10 (4)	4 (1)	4 (1)	3 (1)
Number of pts with E	206 (75)	202 (75)	201 (74)	248 (87)	257 (90)	256 (89)
Number (%) worsened at Wk 52	3 (1)	4 (1)	6 (2)	2 (1)	1 (0.4)	0
p-value of difference		0.7230	0.3392		1.0000	0.2461
BILAG: Vasculitis						
Baseline Domain Score	n = 268	n = 262	n = 270	n = 280	n = 281	n = 274
Number of pts with B	23 (9)	14 (5)	15 (6)	15 (5)	18 (6)	17 (6)
Number of pts with C	106 (40)	113 (43)	108 (40)	102 (36)	100 (36)	88 (32)
Number of pts with D	4 (1)	6 (2)	10 (4)	6 (2)	8 (3)	5 (2)
Number of pts with E	135 (50)	129 (49)	137 (51)	157 (56)	155 (55)	164 (60)
Number (%) worsened at Wk 52	5 (2)	1 (0.4)	1 (0.4)	4 (1)	1 (0.4)	2 (1)
p-value of difference		0.2163	0.1219		0.2162	0.6859
BILAG: Renal						
Baseline Domain Score	n = 275	n = 270	n = 272	n = 286	n = 283	n = 288
Number of pts with B	21 (8)	13 (5)	23 (8)	37 (13)	43 (15)	32 (11)
Number of pts with C	68 (25)	60 (22)	57 (21)	90 (31)	79 (28)	87 (30)
Number of pts with D	13 (5)	16 (6)	15 (6)	23 (8)	20 (7)	17 (6)
Number of pts with E	173 (63)	181 (67)	177 (65)	136 (48)	141 (50)	152 (53)
Number (%) worsened at Wk 52	23 (8)	10 (4)	14 (5)	19 (7)	17 (6)	20 (7)
p-value of difference		**0.0208**	0.1323		0.7552	0.8860
BILAG: Hematology						
Baseline Domain Score	n = 275	n = 271	n = 272	n = 286	n = 286	n = 287
Number of pts with B	36 (13)	40 (15)	34 (12.5)	51 (18)	54 (19)	50 (17)
Number of pts with C	79 (29)	72 (27)	84 (31)	63 (22)	67 (23)	77 (27)
Number of pts with D	21 (8)	17 (6)	17 (6)	12 (4)	16 (6)	24 (8)
Number of pts with E	139 (51)	142 (52)	137 (50)	160 (56)	149 (52)	136 (47)
Number (%) worsened at Wk 52	26 (9)	11 (4)	16 (6)	25 (9)	20 (7)	21 (7)
p-value of difference		**0.0110**	0.1150		0.4370	0.5302

Source: Tables T39, T41, T43, T45, T47, T49, T51, T53 from Summary of Clinical Efficacy Appendices

Dropouts/Medication failure = no improvement

P-values were from likelihood ratio test or Fisher's exact test for individual studies

Whereas instruments such as SLEDAI and BILAG assess disease activity, they do not capture accumulated damage in SLE, which is an important factor related to overall morbidity and ultimately prognosis. To this end, the American College of Rheumatology and European counterparts developed a damage index to capture permanent end-organ-dysfunction in 12 different organ systems affected by SLE:

Table 29: Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology Damage Index for SLE

Item	Score
Ocular (either eye, by clinical assessment)	
Any cataract ever	1
Retinal change *or* optic atrophy	1
Neuropsychiatric	
Cognitive impairment (e.g., memory deficit, difficulty with calculation, poor concentration, difficulty in spoken or written language, impaired performance level) *or* major psychosis	1
Seizures requiring therapy for 6 months	1
Cerebrovascular accident ever (score 2 if >1)	1 (2)
Cranial or peripheral neuropathy (excluding optic)	1
Transverse myelitis	1
Renal	
Estimated or measured glomerular filtration rate <50%	1
Proteinuria ≥3.5 gm/24 hours	1
or	
End-stage renal disease (regardless of dialysis or transplantation)	3
Pulmonary	
Pulmonary hypertension (right ventricular prominence, or loud P2)	1
Pulmonary fibrosis (physical and radiograph)	1
Shrinking lung (radiograph)	1
Pleural fibrosis (radiograph)	1
Pulmonary infarction (radiograph)	1
Cardiovascular	
Angina *or* coronary artery bypass	1
Myocardial infarction ever (score 2 if >1)	1 (2)
Cardiomyopathy (ventricular dysfunction)	1
Valvular disease (diastolic, murmur, or systolic murmur >3/6)	1
Pericarditis for 6 months, *or* pericardiectomy	1
Peripheral vascular	
Claudication for 6 months	1
Minor tissue loss (pulp space)	1
Significant tissue loss ever (e.g., loss of digit or limb) (score 2 if >1 site)	1 (2)
Venous thrombosis with swelling, ulceration, *or* venous stasis	1
Gastrointestinal	
Infarction or resection of bowel below duodenum, spleen, liver, or gall bladder ever, for cause any (score 2 if >1 site)	1 (2)
Mesenteric insufficiency	1
Chronic peritonitis	1
Stricture *or* upper gastrointestinal tract surgery ever	1
Musculoskeletal	
Muscle atrophy or weakness	1
Deforming or erosive arthritis (including reducible deformities, excluding avascular necrosis)	1
Osteoporosis with fracture or vertebral collapse (excluding avascular necrosis)	1
Avascular necrosis (score 2 if >1)	1 (2)
Osteomyelitis	1
Skin	
Scarring chronic alopecia	1
Extensive scarring or panniculum other than scalp and pulp space	1
Skin ulceration (excluding thrombosis) for >6 months	1
Premature gonadal failure	1
Diabetes (regardless of treatment)	1
Malignancy (exclude dysplasia) (score 2 if >1 site)	1 (2)

* Damage (nonreversible change, not related to active inflammation) occurring since onset of lupus, ascertained by clinical assessment and present for at least **6 months** unless otherwise stated. Repeat episodes must occur at least 6 months apart to score 2. The same lesion cannot be scored twice.

Source: Gladman et al. Arthritis & Rheum, March 1996, 39(3):363-369.

The SLICC/ACR Damage Index records damage occurring in patients with SLE regardless of the cause. The damage index does not include hematologic items, such as cytopenias, since these can be waxing and waning phenomena; other manifestations need to have been present for at least 6 months. As shown in Table 30, the results were not consistent with respect to progression in the damage index and therefore definitive conclusions cannot be made.

Table 30: Change in SLICC/ACR Damage Index at Week 52

Change in SLICC/ACR Damage Index at Week 52						
	Study 1056			Study 1057		
	Placebo n = 275	1 mg/kg n = 271	10 mg/kg n = 273	Placebo n = 287	1 mg/kg n = 288	10 mg/kg n = 290
Baseline						
mean (±SE)	0.99 (0.09)	1.04 (0.08)	0.94 (0.08)	0.55 (0.05)	0.60 (0.06)	0.55 (0.06)
Change at Week 52						
mean (±SE)	0.06 (0.02)	0.04 (0.02)	0.04 (0.01)	0.05 (0.02)	0.07 (0.02)	0.03 (0.01)
LS mean (±SE)	0.08 (0.03)	0.07 (0.03)	0.06 (0.03)	0.1 (0.02)	0.12 (0.02)	0.08 (0.02)
p-value (diff vs pbo)		0.5136	0.3415		0.3278	0.4222

Source: Table T37 in Summary of Clinical Efficacy Appendices

Patient Reported Outcomes:

Another prespecified major secondary endpoint was the change from baseline to Week 24 in the SF-36 physical component score (PCS) for the belimumab groups as compared to placebo for both trials. As shown in Table 31, the change from baseline to Week 24 in the SF-36 physical component score (PCS) was comparable for all three treatment groups.

Table 31: Mean Change in SF-36 PCS Score from Baseline to Week 24 (LOCF)

	Trial 1056			Trial 1057		
	Placebo (N=275)	**Belimumab 1mg/kg (N=271)**	**Belimumab 10 mg/kg (N=273)**	**Placebo (N=287)**	**Belimumab 1mg/kg (N=288)**	**Belimumab 10 mg/kg (N=290)**
Mean ± SE	3.36 ± 0.51	3.78 ± 0.46	3.22 ± 0.43	3.64 ± 0.42	3.65 ± 0.43	3.58 ± 0.46
LS Mean ± SE[1]	5.63 ± 0.74	6.16 ± 0.75	5.36 ± 0.72	3.26 ± 0.54	3.39 ± 0.53	3.34 ± 0.55
Treat. Diff. (95% CI)[1] vs PLO		0.53 (-0.67, 1.74)	-0.27 (-1.48, 0.94)		0.13 (-0.95, 1.21)	0.08 (-1.00, 1.15)
P-value[1]		**0.3848**	**0.6601**		**0.8127**	**0.8870**

[1]All statistics, including the difference in LSM (least square means), were from ANCOVA model for the comparison between each belimumab dose and placebo, adjusted for the baseline PCS score and baseline stratification factors. Adapted Sponsor's Table 8-1; p. 147. Adapted Sponsor's Table 8-1; p. 127

Efficacy Conclusions

Although Studies 1056 and 1057 demonstrated a statistically significant increase in belimumab-treated patients achieving a response, defined as a 4-point reduction in the SELENA-SLEDAI, no worsening in the physician global assessment, and no new 1A/2B BILAG domain scores, there are a number of findings in these studies that also raise questions regarding the efficacy of belimumab:

- Lack of a consistent dose-response effect—in some analyses, 1 mg/kg appears to provide a greater treatment effect than 10 mg/kg and in other analyses, 10 mg/kg

appears to be more effective, e.g., SRI Subcomponents (Table 10), SLE Flares (Table 20).
- Lack of statistical significance for Responder Index results at Week 76 (Table 17)
- Lack of statistical significance in increasing the proportion of patients able to reduce prednisone by at least 25% to less than 7.5 mg/day (Table 18)
- Lack of consistency between studies—e.g. reduction in BILAG flares (Table 22), 10 mg/kg increased time to BILAG flare in Study 1057 but not Study 1056; change in PGA (Table 10)—1 mg/kg better in Study 1056 and 10 mg/kg better in Study 1057; effect in the Native American subgroup (Table 15)—favorable in Study 1057, unfavorable in Study 1056.
- Lack of efficacy for the African heritage subgroup of both studies (Table 15)

On the other hand, post-hoc exploratory analyses of the effect of treatment on various organ system manifestations overall appear to be suggestive of a treatment benefit with belimumab (Tables 25 to 28). Some inconsistencies were again noted, but as the numbers of patients with particular organ system involvement was small in most cases, it is difficult to draw definitive conclusions.

The evidence for the efficacy of belimumab in the treatment of SLE is far from consistent and unquestionable. There could be a number of reasons for this, but discussion would be primarily speculative. Given the data as they are, a more relevant question is whether the degree of efficacy demonstrated is worth the apparent risks of treatment, and whether they are worth the anticipated risk of treatment if other immunosuppressives are required to treat serious SLE manifestations.

Review of Safety

Discussion of Clinical Studies Used to Evaluate Safety

This application contained 52-weeks of double-blind safety data generated from the following 3 trials: LBSL02, 1056 and 1057. These trials were of sufficiently similar design to allow for pooled analyses of the controlled safety data by treatment group. It should be noted, however, that the 4 mg/kg belimumab group was only present in Study LBSL02, which evaluated a somewhat different population of SLE patients (including approximately 30% ANA negative patients) than did Studies 1056 and 1057.

Since 1056 was a 76-week study, interim safety data from Week 53 through Week 76 as of the cut-off date June 25, 2009 were also provided in the summary. Additional interim long term safety data generated from the 24-week extension of LBSL02 and the ongoing open-label extension study LBSL99 were also provided in the BLA with a cut-off date of March 6, 2009. Reports of serious adverse events that occurred in ongoing SLE trials (e.g., LBSL99, 1056, 1066 and 1074) after these cut-off dates through December 31, 2009 were also included. The focus of this safety discussion will be on analyses of the pooled data from the three double-blind studies supported by interim safety data in areas that have been identified by the Agency of potential concern.

The Applicant also provided safety data from the single or multiple dosing Phase 1 and Phase 2 studies (LBSL01, 1058, and1070) from their SLE clinical development plan. Since the data from these trials were associated with a different route of administration (e.g., subcutaneous injection), or doses or regimens not under consideration for marketing, these data as well as safety data from the RA clinical development program (Studies LBRA01 and LBRA99) and investigator-initiated trials (e.g., 2 trials in Sjogren's syndrome, 2 trials in pre-renal transplant desensitization and 1 trial in Waldenstrőm's macroglobulinemia) are only considered where pertinent in the discussion that follows.

Deaths and SAEs occurring through July 9, 2010 from ongoing trials in the SLE (LBSL99, 1056, 1066, 1074 and 1070), RA (1089), as well as the 5 investigator-initiated trials with belimumab, were submitted in the 120-day safety update on October 6, 2010 and are included as applicable to the following discussion.

At the time of data cut-off for the ongoing trials LBSL99 and 1056 (June 25, 2009), the extent of exposure to intravenous (IV) belimumab for the five multiple dosing SLE studies was as shown in Table 32 below. A total of 1,603 patients with SLE had been exposed to belimumab in these trials, out of which 946 patients had been treated with the to-be-marketed dose of 10 mg/kg. Approximately 828 of these subjects had received 10 mg/kg of belimumab for ≥ 6 months, 677 subjects for ≥ 12 months, and 73 patients ≥ 24 months. These numbers exceed minimum safety database recommendations for chronic use products as outlined in the ICH E1A guidance document.

Table 32: Exposure to Belimumab in the IV SLE studies (LBSL01, LBSL02, LBSL99, 1056 & 1057)

	1mg/kg N=688	4 mg/kg N=125	10 mg/kg[2] N=946	20 mg/kg N=14	All Active N=1603[3]
Duration of Exposure (days):					
Mean (SD)	359 (131)	358 (165)	620 (495)	38 (11)	548 (487)
Median (Min, Max)	370 (28, 625)	393 (28, 589)	392 (28, 1933)	38 (28, 50)	371 (28, 1937)
Duration of Exposure[1] (months):					
≥ 3	637 (93%)	106 (85%)	876 (93%)	--	1463 (91%)
≥ 6	604 (88%)	102 (82%)	828 (88%)	--	1386 (87%)
≥ 9	566 (82%)	99 (79%)	779 (82%)	--	1302 (81%)
≥ 12	473 (69%)	93 (74%)	677 (72%)	--	1107 (69%)
≥ 18	20 (3%)	23 (18%)	271 (29%)	--	297 (19%)
≥ 24	--	--	257 (27%)	--	274 (17%)
≥ 30	--	--	242 (26%)	--	257 (16%)
≥ 36	--	--	226 (24%)	--	248 (16%)
≥ 42	--	--	181 (19%)	--	229 (14%)
≥ 48	--	--	73 (8%)	--	175 (11%)
≥ 54	--	--	53 (6%)	--	151 (9%)
≥ 60	--	--	16 (2%)	--	38 (2%)

[1]Duration is calculated as last infusion date – first infusion date = 28 days. A 3-month interval is defined as 13 weeks.
[2]Includes subjects who were randomized to the 10mg/kg group and subjects who switched to the 10mg/kg group. For subjects who switched to the 10mg/kg, exposure was calculated after their 1st dose of 10mg/kg belimumab treatment.
[3]In the "10mg/kg" column: Only the exposure to belimumab 10 mg/kg treatment was counted. In the "All Active column" : For patients who switched to belimumab 10 mg/kg group from belimumab 1 mg/kg or 4 mg/kg groups, the initial exposure to belimumab 1 mg/kg or 4 mg/kg treatment was counted in addition to the exposure to belimumab 10 mg/kg treatment.
Adapted Sponosor's Table T5; Appendix 15 of the Summary of Clinical Safety.

Safety overview

All safety analyses were performed on the population who received at least 1 infusion of study medication. Table 33 summarizes adverse events (AEs) that were reported in the belimumab pooled safety database for the controlled SLE trials (LBSL02, 1056 and 1057) by treatment group. The majority of patients in these studies experienced at least one AE during the course of the trial. The proportions of patients experiencing an AE or a serious AE in the belimumab treatment groups were similar to that of placebo. The proportion of patients with at least infection was slightly higher in the 4 mg/kg belimumab group as compared to the 1m/kg and 10mg/kg belimumab groups and placebo, but was not increased for the number of subjects with serious infections. Overall, the number of malignancies observed in the controlled studies was low and comparable across treatment groups. A higher proportion of patients in the 4 mg/kg belimumab group had an AE that resulted in an interruption of study dosing as compared to the other belimumab treatment groups and placebo however, the proportion of subjects who prematurely discontinued treatment was lowest in the 4 mg/kg group as compared to the comparable rates in the other treatment groups. Numerically more deaths occurred during the controlled studies in the 1mg/kg and 10 mg/kg belimumab treatment groups as compared to the placebo group. These deaths will be discussed further below.

Table 33: Summary of Adverse Events and Deaths in the Controlled Studies (LBSL02, 1056 & 1057)

	Placebo N=675	Belimumab 1mg/kg N=673	Belimumab 4 mg/kg N=111	Belimumab 10mg/kg N=674	Total Belimumab N= 1458
Number of Subjects with at Least 1 AE	624 (92%)	626 (93%)	107 (96%)	625 (93%)	1358 (93%)
Number of Subjects with At Least 1 Serious AE	107 (16%)	125 (19%)	15 (14%)	117 (17%)	257 (18%)
Number of Subjects with at Least 1 Infection	450 (67%)	478 (71%)	88 (79%)	471 (70%)	1037 (71%)
Number of Subjects with at Least 1 Serious Infection	35 (5%)	46 (7%)	7 (6%)	35 (5%)	88 (6%)
Number of Subjects with at Least 1 Malignancy	3 (0.4%)	3 (0.4%)	0	3 (0.4%)	6 (0.4%)
Number of Subjects with at Least 1 AE Leading to Dosing Interruption	85 (13%)	86 (13%)	25 (23%)	91 (14%)	202 (14%)
Number of Subjects with at Least 1 AE Leading to Discontinuation	48 (7%)	42 (6%)	4 (4%)	45 (7%)	91 (6%)
Deaths	3 (0.4%)	6* (0.9%)	--	6 (0.9%)	12 (0.8%)

Source: Table 2.7.4-8 of Summary of Clinical Safety
*One SLE –related death occurred more than 15 weeks after patients' last dose of belimumab—per Sponsor's AC briefing document.

Deaths

There were 14 deaths reported in the controlled period of the IV SLE trials, with one additional death occurring in a patient 15 weeks post treatment discontinuation, for a total of 15 deaths, as follows: 3 patients died of cardiovascular (including stroke) events, 5 patients died of infectious etiologies, 2 patients committed suicide, 2 patients died of unknown causes, 2 patients died of SLE-related complications, and 1 patient died of a

malignancy. Table 34 below lists these 15 deaths and the 15 deaths that occurred in the open-label extension studies and RA clinical development program, by treatment group.

Table 34 Deaths in the SLE Studies

Subject Number	Age/Sex	Cause of Death	Days Since 1st Infusion	Days Since Last Infusion	Pertinent History
Placebo					
CL002-001	45yo/F	Myocardial Infarction	328	19	Presented to ER with new onset chest and epigastric pain and had a cardiopulmonary arrest.
CO001-016	25yo/F	Cardiac Arrest Secondary to Sepsis	70	11	Concomitant Meds: Prednisolone, methotrexate, diclofenac and ibuprofen. Developed bacterial gastroenteritis and dehydration complicated by vasculitis and became septic (blood culture positive for Staph. Saprophyticus) despite antibiotics and supportive medical care.
IN005-015	18yo/F	Unknown	225	84	Hospitalized 2 months prior to death for acute abdominal pain secondary to portal/mesenteric/renal vein and vena cava thrombosis and acute pancreatitis.
Belimumab 1 mg/kg					
US034-002	43yo/F	Suicide	32	20	H/O Depression on antidepressant (citalopram). Reported to have worsening depression prior to committing suicide
US014-006	46yo/F	Unknown	56	28	H/O Asthma, clostridial gastroenteritis, eosinophilia and QT prolongation on EKG. Concomitant Meds: ibuprofen, hydroxychloroquine, mycophenolate, prednisone and lisinopril. Pt. developed nausea, vomiting and weakness while camping and was found to be dehydrated due to unspecified gastrointestinal illness at local ER where she died despite resuscitative measures.
US042-006	52yo/F	Ovarian Cancer	21	7	Positive family H/O ovarian cancer. H/O Vaginal bleeding prior to study entry that evolved to include left lower abdominal pain, vaginal pain, pelvic cramping and diarrhea by the 9th dose of study medication that was followed by a diagnosis of advanced ovarian cancer on laporotomy.
AR005-006	32yo/F	Sepsis Secondary to Cellulitis	13	13	Concomitant Meds: Methylprednisolone, mycophenolate, thalidomide, and ibuprofen. Developed cellulitis and died as a result of sepsis despite antibiotics and supportive medical care.
RU005-010	58yo/F	Ischemic Stroke	345	34	H/O hypertension. Anti-cardiolipin antibody negative at screening. Concomitant meds: Prednisolone, hydroxychloroquine, bioprolol.
CL001-007	25yo/F	Respiratory Failure/SLE Flare	216	104	Patient died due to respiratory arrest more than 15 weeks after the patient discontinued the trial due to acute renal failure. Post study withdrawal, the patient was hospitalized and experienced oliguria, uremic syndrome, sepsis, polyserositis, ascites, intestinal edema, anemia, and alveolar hemorrhage.
Belimumab 10 mg/kg					
US041-013	40yo/F	Respiratory Failure Secondary to Sepsis	257	33	Pt. developed aspiration pneumonia status post seizure, became septic and died due to respiratory failure despite antibiotics and aggressive supportive medical care (respirator).
MX001-005	47yo/F	Cardiac Arrest (SLE Flare)	77	21	H/O Diabetes mellitus, pericardial excision, serositis, antiphospholipid syndrome, pulmonary hypertension, and heart failure. Concomitant Meds: Azathioprine, methotrexate and prednisone. Hospitalized after c/o severe headache with vomiting associated with fever, chills and productive cough with bilateral pleural effusions and lymphopenia attributed to SLE flare with CNS involvement. She was treated with corticosteroids and NSAIDs but died due to cardiac arrest.
CL001-024	53yo/F	Bacterial Sepsis	331	25	H/O Obesity, pulmonary fibrosis. Developed septic shock (blood cultures positive for MRSA) and multi-organ failure secondary to infected herpes zoster lesions despite antibiotics. Concomitant meds: Methyplprednisone, azathioprine,

					chloroquine, salbutamol, acenocoumarol, sertraline, and omeprazole
IN004-002	20yo/F	Infectious Diarrhea	336	28	Had SLE flare with cutaneous vasculitis and hypochromic anemia. Started on antibiotics and increased corticosteroids but developed infectious diarrhea and died en route to hospital. Concomitant meds: Prednisolone, azathioprine, hydroxychloroquine, levofloxacin, iron, ciprofloxin/tinidazole, and fluconazole.
KR008-001	23yo/F	Suicide	272	13	H/O Depressed mood and psychotic disorder; autoimmune thyroiditis, and drug-induced hepatitis. Committed suicide following conflict with parent. Concomitant meds: methylprednisone, azathioprine, hydroxychloroquine, meloxicam, levothyroxine, and rebamipide
PE002-001	33yo/F	Respiratory Failure From Presumed Pulmonary Embolus	128	8	H/O chronic cholecystitis. Pt. developed dyspnea eight days after her last study infusion and died en route to the hospital. (No autopsy.) Concomitant meds: Prednisone, levothyroxine, and ceftriaxone.
OLE Trial LBSL99 (Belimumab 10 mg/kg)					
US023-005	65yo/F	Suicide	200	25	H/O Hypertension, fibromyalgia, insomnia and ruptured cerebral aneurysm. Negative history of depression. Death attributed to oxycodone and alcohol intoxication. Concomitant meds: Hydroxychloroquine, valsartan, HCTZ, celecoxib, oxycodone, cyclobenzaprine, trazadone, and APAP/codeine.
US032-002	64yo/F	CMV pneumonia	703	32	Diagnosed with pulmonary fibrosis and pneumonitis. Pt. developed pneumonia secondary to CMV and died despite antivirals, antibiotics, and steroids. Concomitant meds: methotrexate, leflunomide, hydroxychloroquine and prednisone.
US062-002	52yo/F	Coronary atherosclerotic heart disease	44	9	H/O Cardiomyopathy, CHF, CAD, CVA, TIA, hypertension and S/P mitral valve replacement. Pt. found dead in bed. Autopsy listed cause of death as coronary artery arteriosclerosis.
US016-007	71yo/M	Cerebral Hemorrhage	1412	424	H/O Hypertension, seizure disorder, ascending aortic aneurysm chronic diarrhea, anemia, colon CA and S/P right colectomy. Pt. developed a fatal cerebral hemorrhage secondary to head trauma sustained in fall following surgery and died. Concomitant meds: Prednisone, hydroxychloroqune, amlodipine, valsartan, atenolol fuosemide, levetiracetam and doxazosin.
OLE Trials 1074 and 1066					
BR002-002	31yo/F	Bronchopneumonia	67	4	H/O Hypertension. Four days after last study infusion was hospitalized for bronchopneumonia. Developed worsening shortness of breath and died. Concomitnat meds: Prednisone, captopril, nifedipine and atenolol.
TW011-017	30yo/F	Pulmonary hemorrhage	101	13	H/O Renal failure secondary to lupus nephritis (class V, stage II), nephritic syndrome, renal vein thrombosis, hypertension. Pt. was hospitalized for worsening renal failure and went on to develop multiple fungal and bacterial infections that resulted in septic shock, multiorgan failure and death despite aggressive medical care, hemodialysis, mechanical ventilation and antibiotics.
PH004-002	23yo/F	Septic Shock	~1.8 years	48	Presented to ER with worsening dyspnea and renal failure, ultimately requiring mechanical ventilation and dialysis. Patient developed hypotension, necrotic vasculitic lesions, and worsening lupus nephritis, followed by multi-organ failure, with positive cultures.
RO007-003	43yo/F	TTP	~2 years		Patient presented with new onset aphasia and confusion, diagnosed with acute neuropsychiatric syndrome, concurrent with severe thrombocytopenia, thrombotic thrombocytopenic purpura, and hemolytic anemia. Patient died of multi-organ failure
PH001-004	39yo/F	Pneumonia	2.2 years	29	Worsening month-long community acquired pneumonia, complicated by DIC, pulmonary embolism and SLE flare (myocarditis, hemolytic anemia, nephritis, and peripheral

					vasculitis). Concomitant meds: Prednisone.
US018-003	69yo/M	Cardiovascular Disease	1.9 years	29	Found unconscious at home, diagnosed with metabolic encephalopathy. Hospitalized with improvement and discharged to skilled nursing facility. Eighteen days after hospital discharge patient was found dead in his apartment. Cardiovascular disease noted on autopsy.
RA Studies: Placebo					
US004-003	51yo/F	Cardiac Arrest	105	22	H/O Hypercholesterolemia, diabetes mellitus, hypothyroidism. Positive family H/O heart disease. Concomitant meds: Auranofin, prednisone, insulin, estrogen, and levothyroxine. Pt. was found dead at home after having 'chest discomfort' for a few days. (No autopsy.)
RA Studies 10mg/kg					
US007-004	51yo/M	Pneumonia	286	176	H/O COPD and pulmonary fibrosis. Concomitant meds: Leflunomide, albuteral, diazepam, carbamazepine, methadone, olanzapine, Phenobarbital, diazepam, tramadol, cyclobenzaprine, exomeprazole and trihexyphenidyl. Pt. died of pneumonia at another hospital.
US040-004	67yo/F	Respiratory Failure	1211	9	H/O COPD, dyspnea on exertion, angina, and coronary artery arteriosclerosis. Pt. developed aspiration pneumonia, pulmonary edema, atelectasis, pleural effusion and sepsis following surgery to repair a hiatal hernia. Died due to worsening respiratory failure.
US016-008	61yo/M	Coronary Artery Thrombosis	46	20	H/O COPD, deep vein thrombosis, pericarditis and vasculitis. Concomitant meds: methorexate, leflunomide, prednisone, chlorpheniramine, and hydrocodone. Pt found dead attributed to acute coronary artery thrombosis on autopsy.
US016-004	49yo/M	Coronary Artery Disease	1521	219	H/O hypothyroidism, kidney stones and migraines. Concomitant meds: Prednisone, pantoprazole and levothyroxine. Pt. found dead attributed to coronary artery disease on autopsy.

Source: Section 2.7.4.2.1.2. of Summary of Clinical Safety and 120-day safety update p. 11

Based on 14 deaths observed in the controlled period of the IV SLE clinical trials, and one death occurring 15 weeks after patient withdrawal, the death incidence rate per 100 subject-years was almost twice as high for belimumab as for placebo treated subjects, as shown in Table 35. Although the types of death are consistent with immunosuppressive therapies and with the risks related to the underlying and concomitant medical conditions, the apparent increased mortality risk with belimumab remains concerning, particularly in light of the marginal efficacy observed. Even if the single patient who died 15 weeks post study withdrawal was removed from the exposure-adjusted analysis, the mortality rate with belimumab remains much higher than for the placebo group (0.73/100 pt-years).

Table 35: Exposure-Adjusted Incidence of Death in the Studies LBSL02, 1056, and 1057

	Placebo	Belimumab
Number of Subjects	**675**	**1458**
Subject-Year	**692**	**1516**
Number of Deaths	**3**	**12**
Death Rate/100 Subject-Years	**0.43**	**0.79**
95% Confidence Interval	**(0.09, 1.27)**	**(0.41, 1.38)**

Adapted Sponsor's Table 10-13, p. 189 of their AC Briefing Package

Analyses that incorporate the uncontrolled-long term extension data are difficult to interpret, given that there may be unquantifiable survival bias related to patients who are in the best condition or tolerating treatment the best remaining in long-term follow-up.

Therefore only the exposure-adjusted incidence from the controlled period of the studies is presented here.

Nonfatal Serious Adverse Events

Malignancy

Because belimumab targets B-cells, immunosuppression is an expected effect, and chronic immunosuppression has been associated with an increase in risk for developing a malignancy. Therefore, the safety database generated from the controlled SLE trials was examined for cases of malignancy. As shown in Table 36, there were a total 9 confirmed malignancies reported during the controlled SLE trials. No discernable pattern for malignancies was observed.

Table 36: Malignancies During the Controlled SLE Studies (LBSL02, 1056, and 1057)

	Placebo (N=675)	Belimumab 1mg/kg (N=673)	Belimumab 4 mg/kg (N=111)	Belimumab 10 mg/kg (N=674)	Total Belimumab N= 1458
Subjects with ≥ 1 Malignancy	**3 (0.4%)**	**3 (0.4%)[1]**	**0**	**3 (0.4%)**	**6 (0.4%)**
Basal cell carcinoma	1 (0.1%)	0	0	1 (0.1%)	1 (0.1%)
Squamous cell carcinoma	0	0	0	2 (0.3%)	2 (0.1%)
Breast cancer	1 (0.1%)	1 (0.1%)	0	0	1 (0.1%
Carcinoid tumor of the stomach	1 (0.1%)	0	0	0	0
Cervical carcinoma (stage 0)	0	1 (0.1%)	0	0	1 (0.1%)
Ovarian cancer	0	1 (0.1%)	0	0	1 (0.1%)

[1]Excludes Subject US052-000009 diagnosed with a thyroid neoplasm

The controlled trials were not designed to determine the risk for developing a malignancy due to exposure to belimumab. Nonetheless, the exposure-adjusted incidence rate for malignancies including and excluding non-melanoma skin cancers was calculated based on the number of cases observed in these studies based on the limited exposure data available. As shown in Table 37, the exposure-adjusted incidence rates for malignancies in both the placebo and combined belimumab treatment groups were low, and did not appear to be increased in the combined belimumab treatment group.

Table 37: Rate of Malignancy in the Studies LBSL02, 1056, and 1057

	Placebo	Belimumab
Number of Subjects	675	1458
Subject-Years	672 subject-years	1473 subject-years
Number of Malignancies[1]	3 (0.4%)	6 (0.4%)
Malignancies/100 Subject-Yrs	0.45	0.41
95% Confidence Interval	(0.09, 1.30)	(0.15, 0.89)
Number of Subjects	675	1458
Subject-Years	672 subject-years	1473 subject-years
Number of Malignancies	2 (0.3%)	3 (0.2%)
Malignancies (excl. NMSC[2])/100 Subject-Yrs	0.30	0.20
95% Confidence Interval	(0.04, 1.07)	(0.04, 0.60)

[1]Includes Subject TW005-002 diagnosed with breast cancer after 2 months S/P completing study.
[2]NMSC = non-melanoma skin cancers
Source: Table 6-2 of Summary of Clinical Safety Appendices

Additional available data from long term extensions and other SLE trials were provided with a data cut-off of December 31, 2009. These data were compared to published estimates of the background rate of cancer in SLE patients. As shown in Table 38 below, the results of this analysis show that incidence rate of malignant neoplasms in the belimumab SLE safety database was similar to that reported in the literature for a large, international cohort of SLE patients.

Table 38: Malignancy Rates Excluding Non-Melanoma Skin Cancers for all Belimumab SLE Trials as of data cut-off date of July 9, 2010

	Background Rate[1]	Belimumab
Number of Subjects	9547	1982
Subject-Years	76,948 subject-years	3976 subject-years
Subjects with Events	410 (4.3%)	18 (0.9%)
Malignancy Rate/100 Subject-Yrs (95% CI)	0.53 (0.48, 0.59)	0.45 (0.27, 0.72)

[1]Bernatsky et al, 2005 (Data from a large, international SLE cohort study. Observed cancers were determined by linkage to regional cancer registries which were not designated to capture non-melanoma skin cancers.
[2]Includes the following subjects with events unspecified as benign or malignant: LBSL99-US040-010 with hepatic and lung neoplasm, LBSL99-US046-029 with lung neoplasm, LBSL99-US007-002 with thyroid and lung neoplasm. Does not include the following subjects with events unspecified as benign or malignant LBSL02-US052-009, LBSL99-US028-001, LBSL99-US031-007 and LBSL99-US045-003 with thyroid neoplasms and LBSL99-US029-001 with soft tissue tumor.
Adapted Sponsor's Table 6-4; Appendix 6 of the Summary of Clinical Safety.

Table 39 below is a tabular summary of all cases of malignancy and neoplasms observed in the belimumab SLE safety database as of the cut-off date of December 31, 2009. The most common malignancies observed in SLE patients exposed to belimumab were squamous cell cancer (4 cases), basal cell cancer (3 cases), breast cancer (3 cases), colon cancer (2 cases), and B-cell lymphoma (2 cases). Of note, there were a total of 5 cases of thyroid neoplasms reported either singly (4 case) or associated with hepatic neoplasm (1 case) in patients treated with belimumab. One out of these 5 cases of thyroid neoplasms (Subject US052-009) occurred during the controlled studies, while the remainder were observed in the open-label studies following prolonged exposure to belimumab. Cases of non-malignant thyroid neoplasm are not unexpected, given the reported increased prevalence of thyroid disorders associated with SLE (ranging from 11.5% to 24%) in the worldwide literature.[6] However there was a numeric imbalance, with more cases occurring in the belimumab treatment arms.

[6] Appenzeller S, Pallone AT, Natalin RA, Costallat LT. Prevalance of Thyroid Dysfunction in Systemic Lupus Erythematosus. J Clin Rheumatol. 2009; 15:117-119.
Lazurova I, Benhatchi K, Rovensky J, Kozakova D, et al. Autoimmune Thyroid Diseae and Autoimmune Rheumatic Disorders: A Two-sided Analysis. Ann NY Acad Sci 2009; 1173:211-216.
Mader R, Mishail S, Adawi M, Lavi I. Luboshitzky R. Thyroid dysfunction in patients with systemic lupus erythematosus (SLE): relation to disease activity. Clin Rheum 2007; 26:1891-1894.

Table 39: Neoplasms in the Belimumab SLE Trials (data cut-off December 31, 2009)

	Placebo	Belimumab 1mg/kg	Belimumab 4 mg/kg	Belimumab 10mg/kg	Total Belimumab
Total Subjects with ≥ 1 Malignancy/Neoplasm	**5**	**4**	**1**	**24**	**29**
Sold Tumors :					
Breast Cancer	1	1	0	2	3
Colon Cancer	0	0	0	2	2
Malignant Melanoma	0	0	0	1	1
Carcinoid Tumor of the Stomach	1	0	0	0	0
Cervical Carcinoma (Stage 0)	0	0	0	0	0
Rectal Cancer	1	1	0	1	2
Renal Cell Carcinoma	0	0	0	1	1
Ovarian Cancer	0	0	0	0	0
Malignant Lung Neoplasm with Mets (Bone/Marrow)	0	1	0	1	2
Hematologic/Lymphatic:					
B-cell Lymphoma	0	0	1	0	1
Nodal Marginal Zone B-cell Lymphoma	0	0	0	1	1
Multiple Myeloma	0	0	0	1	1
Non-Melanoma Skin Cancer:					
Basal Cell Carcinoma	1	0	0	3	3
Squamous Cell Carcinoma	0	0	0	4	4
Solid Tumors of Unspecified Classification:					
Hepatic and Lung Neoplasm	0	0	0	1	1
Lung and Thyroid Neoplasm	0	0	0	1	1
Lung Neoplasm	0	0	0	1	1
Thyroid Neoplasm	0	1	0	3	4
Soft Tissue Neoplasm	0	0	0	1	1
Breast Neoplasm	1	0	0	0	0

Reviewer's table based on Sponsor's Table 6-1; Appendix 6 of Summary of Clinical Safety Appendices

In the 120-day safety update, data cut-off 9 July 2010, there were three new malignancies reported: an SLE patient with MALT type B cell lymphoma, an SLE patient with a malignant thymoma, and 1 RA patient with a B cell lymphoma.

Serious Infections

Because of its mechanism of action, belimumab would also be anticipated to increase the risk of infections, including serious infection. In fact, as shown in Table 40 below, infections were the most common system-organ-class (SOC) reported, and the exposure-adjusted-incidence of serious infection was higher in the combined belimumab groups compared to placebo (5.2 vs. 6.0 infections per 100 patient-years for placebo and belimumab groups, respectively).

Table 40: Serious Infections in Studies LBSL02, 1056 and 1057

	Placebo N=675	Belimumab 1mg/kg N=673	Belimumab 4 mg/kg N=111	Belimumab 10mg/kg N=674	Total Belimumab N= 1458
Serious Infections Totals, n (%)	**35 (5)**	**46 (7)**	**7 (6)**	**35 (5)**	**88 (6)**
Exposure-Adjusted Incidence (per 100 patient-years)	5.2				6.0
Cases of Sepsis	3 (0.4)	4 (0.6)	1 (0.9)	5 (0.7)	10 (0.7)
Most Common Preferred Terms					
Pneumonia	10 (1.5)	7 (1.0)	1 (0.9)	6 (0.9)	14 (1.0)
Urinary Tract Infection	4 (0.6)	7 (1.0)	1 (0.9)	5 (0.7)	13 (0.9)
Cellulitis	2 (0.6)	7 (1.0)	1 (0.9)	1 (0.1)	9 (0.6)
Bronchitis	1 (0.1)	2 (0.3)	1 (0.9)	3 (0.4)	6 (0.4)
Pyelonephritis	3 (0.4)	3 (0.4)	0	0	3 (0.2)

Source: Appendix Table 10.1 and Table 2.7.4-26 of Summary of Clinical Safety
Exposure is 672.3 subject-years for placebo and 1472.9 subject-years for combined belimumab groups

Unusual infections included: 1 case of West Nile virus infection occurring in a patient treated with belimumab 4 mg/kg; 1 case of disseminated herpes zoster occurring in a patient on belimumab 10 mg/kg; 1 case of disseminated cytomegaloviral infection occurring in a patient on belimumab 10 mg/kg, 1 case of Dengue Fever occurring in a patient on belimumab 1 mg/kg, and 1 case of clostridium difficile colitis in a patient on belimumab 10 mg/kg. Two cases of severe acinetobacter infection were observed—the first was a case of Acinetobacter bactermia occurring in a patient receiving belimumab 10 mg/kg, and the second was a case *Acinetobacter iwolfii* pneumonia in a patient receiving belimumab 1 mg/kg. In the 120-day safety update, 4 new cases of mycobacterial infection (3 cases of TB and 1 case of atypical mycobacterial infection) were reported in SLE patients participating in the open-label continuation studies in endemic areas—3 patients were on 10 mg/kg of belimumab and one patient was on 1 mg/kg.

Serious Adverse Events

Table 41 is an abridged summary of the serious adverse events (SAE) observed during the controlled IV SLE studies. Overall, the proportions of patients who had a SAE were similar for the placebo and belimumab treatment groups with a slightly higher number of SAEs reported in the belimumab 1 mg/kg group. Numeric imbalances in the number of SAEs were noted, with a higher incidence in the 10 mg/kg belimumab treatment group as compared to placebo in the following system organ classes: Blood and Lymphatic System disorders, General Disorders and Administration Site Conditions, Immune System Disorders, Infections and Infestations, Nervous System Disorders, Pregnancy, Puerperium and Perinatal Conditions, Psychiatric Disorders, Renal and Urinary disorders, Reproductive System and Breast Disorders, and Vascular Disorders. Serious adverse events related to infections, immune system, nervous and psychiatric disorders are discussed separately in other sections of this review.

Table 41: Serious Adverse Events in Studies LBSL02, 1056 and 1057

MedDRA System Organ Class	Placebo N=675	Belimumab 1mg/kg N=673	Belimumab 4 mg/kg N=111	Belimumab 10mg/kg N=674	Total Belimumab N= 1458
Number of Subjects with ≥ 1 SAE: Exposure-Adjusted Incidence[1] per 100 patient-years	**107 (16%) 15.9**	**125 (19%)**	**15 (14%)**	**117 (17%)**	**257 (18%) 17.4**
Blood and Lymphatic System Dis.:	**7 (1%)**	**4 (1%)**	**0**	**11 (2%)**	**15 (1%)**
Anemia	1 (0.1%)	2 (0.3%)	0	6 (0.9%)	8 (0.5%)
Thrombocytopenia	2 (0.3%)	1 (0.1%)	0	2 (0.3%)	3 (0.2%)
Hemolytic Anemia	2 (0.3%)	0	0	2 (0.3%)	2 (0.1%)
Neutropenia	1 (0.1%)	1 (0.1%)	0	1 (0.1%)	2 (0.1%)
Febrile Neutropenia	0	1 (0.1%)	0	1 (0.1%)	2 (0.1%)
Lymphopenia	0	0	0	2 (0.3%)	2 (0.1%)
Hypochromic anemia	0	0	0	1 (0.1%)	1 (0.7%)
Leukopenia	0	1 (0.1%)	0	0	1 (0.7%)
Thymus Enlargement	0	0	0	1 (0.1%)	1 (0.7%)
Cardiac Disorders	**13 (2%)**	**6 (1%)**	**2 (10%)**	**11 (2%)**	**19 (1.3%)**
Ear and Labyrinth Disorders	**0**	**1 (0.1%)**	**0**	**0**	**1 (0.07%)**
Endocrine Disorders:	**0**	**2 (0.3%)**	**0**	**1 (0.1%)**	**3 (0.2%)**
Hypothyroidism	0	2 (0.3%)	0	0	2 (0.1%)
Adrenal Insufficiency	0	0	0	1 (0.1%)	1 (0.1%)
Eye Disorders	**0**	**2 (0.3%)**	**0**	**1 (0.1%)**	**3 (0.2%)**
Gastrointestinal Disorders	**17 (3%)**	**13 (2%)**	**3 (3%)**	**10 (2%)**	**26 (2%)**
General Disorders and Administrative Site Conditions:	**13 (2%)**	**10 (2%)**	**0**	**17 (3%)**	**27 (2%)**
Pyrexia	3 (0.4%)	5 (0.7%)	0	9 (1.3%)	14 (1.0%)
Infusion Related Reaction	2 (0.3%)	2 (0.3%)	0	4 (0.6%)	6 (0.4%)
Non-Cardiac Chest Pain	5 (0.7%)	1 (0.1%)	0	2 (0.3%)	3 (0.2%)
Death	1 (0.1%)	1 (0.1%)	0	0	1 (0.1%)
Fatigue	1 (0.1%)	1 (0.1%)	0	0	1 (0.1%)
Chest pain	0	0	0	1 (0.1%)	1 (0.1%)
Chills	0	1 (0.1%)	0	0	1 (0.1%)
Edema Peripheral	0	0	0	1 (0.1%)	1 (0.1%)
Hepatobiliary Disorders:	**6 (1%)**	**8 (1%)**	**2 (2%)**	**5 (1%)**	**15 (1%)**
Immune System Disorders:	**1 (0.1%)**	**2 (0.3%)**	**0**	**2 (0.3%)**	**4 (0.3%)**
Anaphylactic Reaction	0	2 (0.3%)	0	1 (0.1%)	3 (0.2%)
Drug Hypersensitivity	0	0	0	1 (0.1%)	1 (0.1%)
Infections and Infestations:	**35 (5%)**	**46 (7%)**	**7 (6%)**	**35 (5%)**	**88 (6.0%)**
Injury, Poisoning and Procedural Complications	**7 (1%)**	**6 (1%)**	**3 (3%)**	**7 (1%)**	**16 (1%)**
Investigations	**1 (0.1%)**	**0**	**0**	**3 (0.4%)**	**3 (0.2%)**
Metabolism and Nutrition Disorders	**3 (0.4%)**	**3 (0.4%)**	**0**	**1 (0.1%)**	**4 (0.3%)**
Musculoskeletal and Connective Tissue Disorder	**14 (2%)**	**16 (2%)**	**1 (1%)**	**13 (2%)**	**30 (2%)**
Neoplasms Benign, Malignant and Unspecified (incl. cysts/polyps)	**3 (0.4%)**	**5 (1%)**	**0**	**1 (0.1%)**	**6 (0.4%)**
Nervous System Disorders:	**8 (1%)**	**10 (2%)**	**1 (1%)**	**16 (2%)**	**27 (2%)**
Pregnancy, Puerperium and Perinatal Conditions:	**1 (0.1%)**	**2 (0.2%)**	**0**	**5 (1%)**	**7 (0.5%)**
Abortion Spontaneous	1 (0.1%)	0	0	5 (1%)	5 (0.3%)
Pregnancy	0	1 (0.1%)	0	0	1 (0.1%)
Psychiatric Disorders	**3 (0.4%)**	**4 (1%)**	**0**	**8 (1%)**	**12 (0.8%)**
Renal and Urinary Disorders:	**12 (2%)**	**9 (1%)**	**0**	**14 (2%)**	**23 (1.6%)**

Lupus Nephritis	5 (0.7%)	5 (0.7%)	0	6 (0.9%)	11 (0.8%)
Proteinuria	2 (0.3%)	0	0	4 (0.6%)	4 (0.3%)
Nephrotic Syndrome	0	1 (0.1%)	0	2 (0.3%)	2 (0.1%)
Cystitis Noninfective	2 (0.3%)	0	0	0	0
Renal Failure	1 (0.1%)	1 (0.1%)	0	1 (0.1%)	2 (0.1%)
Calculus Ureteric	0	0	0	1 (0.1%)	1 (0.1%)
Cystitis Hemorrhagic	0	1 (0.1%)	0	0	1 (0.1%)
Diabetic Nephropathy	0	0	0	1 (0.1%)	1 (0.1%)
Glomerulonephritis	1 (0.1%)	0	0	0	0
Glomerulonephritis Membranous	0	0	0	1 (0.1%)	1 (0.1%)
Hematuria	0	1 (0.1%)	0	0	1 (0.1%)
Nephrolithiasis	0	1 (0.1%)	0	0	1 (0.1%)
Renal Vein Thrombosis	1 (0.1%)	0	0	0	0
Reproductive System and Breast Disorders:	5 (1%)	3 (0.4%)	0	7 (1%)	10 (0.7%)
Cervical Dysplasia	1 (0.1%)	2 (0.3%)	0	1 (0.1%)	3 (0.2%)
Menorrhagia	1 (0.1%)	0	0	1 (0.1%)	1 (0.1%)
Ovarian Cyst	1 (0.1%)	0	0	1 (0.1%)	1 (0.1%)
Cerival Disorder	0	0	0	1 (0.1%)	1 (0.1%)
Cystocele	0	0	0	1 (0.1%)	1 (0.1%)
Menometrorrhagia	0	0	0	1 (0.1%)	1 (0.1%)
Postmenopausal Hemorrhage	1 (0.1%)	0	0	0	0
Uterine Hemorrhage	0	1 (0.1%)	0	0	1 (0.1%)
Uterine Polyp	0	0	0	1 (0.1%)	1 (0.1%)
Uterovaginal Prolapse	0	0	0	1 (0.1%)	1 (0.1%)
Vaginal Hemorrhage	1 (0.1%)	0	0	0	0
Vulvar Dysplasia	0	0	0	1 (0.1%)	1 (0.1%)
Respiratory, Thoracic and Mediastinal Disorders	**11 (2%)**	**7 (1%)**	**1 (1%)**	**8 (1%)**	**16 (1.1%)**
Skin and Subcutaneous Tissue Disorders	**6 (1%)**	**5 (1%)**	**0**	**5 (1%)**	**10 (0.7%)**
Surgical and Medical Procedures	**1 (0.1%)**	**0**	**0**	**0**	**0**
Vascular Disorders:	**7 (1%)**	**6 (1%)**	**2 (2%)**	**11(2%)**	**19 (1.3%)**
Deep Vein Thrombosis	1 (0.1%)	0	0	3 (0.4%)	3 (0.2%)
Hypertension	1 (0.1%)	1(0.1%)	0	1 (0.1%)	2 (0.1%)
Hypertensive Crisis	0	0	0	3 (0.4%)	3 (0.2%)
Hypotension	1 (0.1%)	1 (0.1%)	0	1 (0.1%)	1 (0.1%)
Vasculitis	1(0.1%)	1 (0.1%)	1 (0.1%)	0	2 (0.1%)
Arteriosclerosis	0	1 (0.1%)	1 (0.1%)	0	2 (0.1%)
Raynaud's Phenomenon	0	1 (0.1%)	0	1 (0.1%)	2 (0.1%)
Thrombophlebitis Superficial	2 (0.3%)	0	0	0	0
Aortic Dissection	0	1 (0.1%)	0	0	1 (0.1%)
Femoral Artery Embolism	0	0	0	1 (0.1%)	1 (0.1%)
Jugular Vein Thrombosis	0	0	0	1 (0.1%)	1 (0.1%)
Subclavian Vein Thrombosis	1 (0.1%)	0	0	0	0
Vena Cava Thrombosis	1(0.1%)	0	0	0	0

Modified Sponsor's Table T62; Appendix 15 of the Summary of Clinical Safety.
[1]Exposure is 672.3 subject-years for placebo and 1472.9 subject-years for combined belimumab groups

It should be noted that many of the SAEs seen in the Blood and Lymphatic System Disorders, Renal and Urinary Disorders and Vascular Disorders SOC are of the type that are known to occur with the underlying disease of SLE (i.e., anemias, leukopenias, lymphopenias, thrombocytopenias, lupus nephritis, glomerulonephritis, proteinuria, thrombotic and embolic events), thus their occurrence is not unexpected. The higher

rates of SAEs observed in the Pregnancy, Puerperium and Perinatal Conditions and Reproductive System and Breast Disorders is not unexpected since the majority of the subjects who participated in these trials are female and of childbearing potential.

The SAE listed under General Disorders and Administration Site Conditions suggest that the higher rate of SAEs attributed to belimumab are primarily due to pyrexia and infusion related reactions, as reported by study investigators. Infusion related reactions are expected AEs associated with infusion of proteins with foreign sequences, such as belimumab; however it is not clear that infusion-related reactions have been classified correctly in every case (see section on anaphylaxis, hypersensitivity and infusion reactions below).

Table 42 lists SAEs that occurred in ≥ 5 subjects treated with belimumab during the controlled IV SLE trials. Pyrexia, urinary tract infection, lupus nephritis, cholelithiasis, cellulitis, and anemia were the most commonly observed SAEs in patients who received belimumab in these trials. As noted previously, the majority of these SAEs could have been related to underlying SLE disease activity or as a result of infections.

Table 42: SAE Preferred Terms Reported by ≥5 Subjects in LBSL02, 1056, and 1057

MedDRA Preferred Term	Placebo N=675	Belimumab 1mg/kg N=673	Belimumab 4 mg/kg N=111	Belimumab 10mg/kg N=674	Total Belimumab N= 1458
Number of Subjects with at Least 1SAE	**107 (16%)**	**125 (19%)**	**15 (14%)**	**117 (17%)**	**257 (18%)**
Pyrexia	3 (0.4%)	5 (0.7%)	0	9 (1.3%)	14 (1.0%)
Urinary Tract Infection	4 (0.6%)	7 (1.0%)	1 (0.9%)	5 (0.7%)	13 (0.9%)
Lupus Nephritis	5 (0.7%)	5 (0.7%)	0	6 (0.9%)	11 (0.8%)
Cholelithiasis	4 (0.6%)	5 (0.7%)	2 (1.8%)	2 (0.3%)	9 (0.7%)
Cellulitis	2 (0.2%)	7 (1.0%)	1 (0.9%)	1 (0.1%)	8 (0.5%)
Anemia	1 (0.1%)	2 (0.3%)	0	6 (0.9%)	8 (0.5%)
Infusion Related Reaction	2 (0.2%)	2 (0.3%)	0	4 (0.4%)	6 (0.4%)
Bronchitis	1 (0.1%)	2 (0.3%)	1 (0.9%)	3 (0.4%)	6 (0.4%)
Depression	1 (0.1%)	3 (0.4%)	0	3 (0.4%)	6 (0.4%)
SLE Arthritis	2 (0.2%)	1 (0.1%)	0	4 (0.6%)	5 (0.3%)
Abortion Spontaneous	1 (0.1%)	1 (0.1%)	0	4 (0.6%)	5 (0.3%)
Osteonecrosis	1 (0.1%)	4 (0.6%)	0	1 (0.1%)	5 (0.3%)

Adapted Sponsor's Table 2.7.4-16; p. 74 of the Summary of Clinical Safety

Overall there was a numeric imbalance, with a higher incidence of SAE occurring with belimumab treatment compared to placebo. Although there are confounding factors, such as less duration of exposure with placebo (e.g., due to drop-out), it is not possible to rule out inherent toxicities associated with belimumab treatment played a major factor in the increased risk observed.

Adverse Events Causing Discontinuation

Table 43 is an abridged summary of adverse events by system organ class and preferred term that resulted in patients discontinuing from the controlled SLE studies LBSL02, 1056, and 1057. Overall, the proportions of patients who discontinued due to an AE were

comparable for the placebo and belimumab 1 mg/kg and 10 mg/kg treatment groups with fewer patients discontinuing study treatment in the 4 mg/kg group as a result of an adverse event. Renal and Urinary Disorders, Nervous System Disorders, Infections and Infestations, Skin and Subcutaneous Tissue and General Disorders and Administrative Site Conditions were the most common types of adverse events resulting in patients withdrawing from these studies. The higher rate of discontinuations from study treatment seen in the Renal and Urinary Disorders was due to flares of lupus nephritis which occurred more frequently in the placebo group as compared to the belimumab treatment groups. Similarly, the higher rate of study discontinuation observed in the Skin and Subcutaneous Tissue Disorders was primarily due to skin manifestations of patients' underlying disease. The higher rate of withdrawal due to Nervous System Disorders is attributable to single cases of adverse events that did not appear to comprise a pattern. Withdrawals due to infection are an expected finding in clinical trials evaluating immunosuppressive therapies.

Table 43: Discontinuations due to Adverse Events in Studies LBSL02, 1056, and 1057

MedDRA System Organ Class/Preferred Term	Placebo N=675	Belimumab 1mg/kg N=673	Belimumab 4 mg/kg N=111	Belimumab 10mg/kg N=674	Total Belimumab N= 1458
Number of Subjects with ≥ 1 AE Leading to Discontinuation:	**48 (7%)**	**42 (6%)**	**4 (4%)**	**45 (7%)**	**91 (6%)**
Blood and Lymphatic System Dis.	4 (0.6%)	0	0	0	0
Cardiac Disorders:	3 (0.4%)	1 (0.1%)	0	3 (0.4%)	4 (0.3%)
Myocardial Infarction	2 (0.3%)	0	0	1 (0.1%)	1 (0.1%)
Cardiac Arrest	1 (0.1%)	0	0	1 (0.1%)	1 (0.1%)
Bradycardia	0	1 (0.1%)	0	0	1 (0.1%)
Pericarditis Lupus	0	0	0	1 (0.1%)	1 (0.1%)
Eye Disorders:	0	1 (0.1%)	0	0	1 (0.1%)
Ocular Vasculitis	0	1 (0.1%)	0	0	1 (0.1%)
Gastrointestinal Disorders:	1 (0.1%)	0	0	1 (0.1%)	1 (0.1%)
Dysphagia	0	0	0	1 (0.1%)	1 (0.1%)
General Disorders and Administrative Site Conditions:	3 (0.4%)	4 (0.6%)	0	5 (0.7%)	9 (0.6%)
Infusion Related Reaction	1 (0.1%)	2 (0.3%)	0	5 (0.7%)	7 (0.5%)
Pyrexia	2 (0.3%)	1 (0.1%)	0	0	1 (0.1%)
Death	0	1 (0.1%	0	0	1 (0.1%)
Hepatobiliary Disorders:	1 (0.1%)	0	1 (0.1%)	0	1 (0.1%)
Cholelithiasis	0	0	1 (0.1%)	0	1 (0.1%)
Immune System Disorders:	0	3 (0.4%)	0	2 (0.3%)	5 (0.3%)
Anaphylactic Reaction	0	1 (0.1%)	0	1 (0.1%)	2 (0.1%)
Drug Hypersensitivity	0	1 (0.1%)	0	1 (0.1%)	2 (0.1%)
Hypogammaglobulinemia	0	1 (0.1%)	0	0	1 (0.1%)
Infections and Infestations:	7 (1.0%)	5(0.7%)	1 (0.9%)	4 (0.6%)	10 (0.7%)
Pneumonia	0	2 (0.3%)	0	1 (0.1%)	3 (0.3%)
Urinary Tract Infection	1 (0.1%)	0	1 (0.1%)	0	1 (0.1%)
Erysipelas	1 (0.1%)	1 (0.1%)	0	0	1 (0.1%)
Furuncle	0	0	0	1 (0.1%)	1 (0.1%)
Herpes Zoster	0	0	0	1 (0.1%)	1 (0.1%)
Kidney Infection	0	0	0	1 (0.1%)	1 (0.1%)
Sepsis	0	1 (0.1%)	0	0	1 (0.1%)
Septic Arthritis Streptococcal	0	1 (0.1%)	0	0	1 (0.1%)
Injury, Poisoning and Procedural Complications:	0	0	1 (0.9%)	0	1 (0.1%)
Road Traffic Accident	0	0	1 (0.9%)	0	1 (0.1%)
Investigations:	0	1 (0.1%)	0	3 (0.4%)	4 (0.3%)
Alanine Aminotransferase Increased	0	0	0	1 (0.1%)	1 (0.1%)

Hepatic Enzyme Increased	0	1(0.1%)	0	0	1 (0.1%)
Weight Decreased	0	0	0	1 (0.1%)	1 (0.1%)
Weight Increased	0	0	0	1 (0.1%)	1 (0.1%)
Musculoskeletal and Connective Tissue Disorder:	5 (0.7%)	2 (0.3%)	0	1 (0.1%)	3 (0.2%)
SLE Arthritis	2 (0.3%)	1 (0.1%)	0	0	1 (0.1%)
Myalgia	2 (0.3%)	0	0	1 (0.1%)	1 (0.1%)
Osteonecrosis	0	1 (0.1%)	0	0	1 (0.1%)
Neoplasms Benign, Malignant and Unspecified (incl. cysts/polyps):	1 (0.1%)	2 (0.3%)	0	0	2 (0.1%)
Breast Cancer	0	1 (0.1%)	0	0	1 (0.1%)
Cervix Carcinoma Stage 0	0	1 (0.1%)	0	0	1 (0.1%)
Nervous System Disorders:	4 (0.4%)	5 (0.7%)	0	6 (0.9%)	11 (0.8%)
Headache	1 (0.1%)	1 (0.1%)	0	1 (0.1%)	2 (0.1%)
Convulsion	0	0	0	1 (0.1%)	1 (0.1%)
Ischemic Stoke	0	1 (0.1%)	0	0	1 (0.1%)
Lupus Encephalitis	0	0	0	1 (0.1%)	1 (0.1%)
Myasthenia Gravis	0	0	0	1 (0.1%)	1 (0.1%)
Myelitis Transverse	0	1 (0.1%)	0	0	1 (0.1%)
Neuritis	0	1 (0.1%)	0	0	1 (0.1%)
Neuropsychiatric Lupus	0	0	0	1 (0.1%)	1 (0.1%)
Peripheral Sensory Neuropathy	0	1 (0.1%)	0	0	1 (0.1%)
Transient Ischemic Attack	0	0	0	1 (0.1%)	1 (0.1%)
Pregnancy, Puerperium and Perinatal Conditions:	2 (0.3%)	2 (0.3%)	0	1 (0.1%)	3 (0.2%)
Pregnancy	1 (0.1%)	2 (0.3%)	0	1 (0.1%)	3 (0.2%)
Psychiatric Disorders:	0	1 (0.1%)	0	2 (0.3%)	3 (0.2%)
Mania	0	1 (0.1%)	0	1 (0.1%)	2 (0.1%)
Completed Suicide	0	0	0	1 (0.1%)	1 (0.1%)
Renal and Urinary Disorders:	8 (1.2%)	6 (0.9%)	0	8 (1.2%)	14 (1%)
Lupus Nephritis	8 (1.2%)	4 (0.6%)	0	6 (0.9%)	10 (0.7%)
Nephropathy	0	1 (0.1%)	0	0	1 (0.1%)
Nephrotic Syndrome	0	0	0	1 (0.1%)	1 (0.1%)
Proteinuria	0	0	0	1 (0.1%)	1 (0.1%)
Renal Failure Acute	0	1 (0.1%)	0	0	1 (0.1%)
Reproductive System and Breast Disorders:	0	1 (0.1%)	0	0	1 (0.1%)
Cervical Dysplasia	0	1 (0.1%)	0	0	1 (0.1%)
Respiratory, Thoracic and Mediastinal Disorders:	2 (0.3%)	2 (0.3%)	0	4 (0.6%)	6 (0.45)
Pleurisy	1 (0.1%)	1 (0.1%)	0	1 (0.1%)	2 (0.1%)
Respiratory Failure	0	0	0	2 (0.3%)	2 (0.2%)
Acute Respiratory Distress Syndrome	0	1 (0.1%)	0	0	1 (0.1%)
Dyspnea	0	0	0	1 (0.1%)	1 (0.1%)
Skin and Subcutaneous Tissue Disorders:	6 (0.9%)	3 (0.4%)	1 (0.9%)	5 (0.7%)	9 (0.6%)
Angioedema	0	1 (0.1%)	1 (0.9%)	1 (0.1%)	3 (0.2%)
Systemic Lupus Erythematosus Rash	2 (0.3%)	0	0	1 (0.1%)	1 (0.1%)
Eczema	1 (0.1%)	0	0	1 (0.1%)	1 (0.1%)
Cutaneous Lupus Erythematosus	0	0	0	1 (0.1%)	1 (0.1%)
Pruritus	0	1 (0.1%)	0	0	1 (0.1%)
Pruritus Allergic	0	1 (0.1%)	0	0	1 (0.1%)
Skin Ulcer	0	0	0	1 (0.1%)	1 (0.1%)
Vascular Disorders:	1 (0.1%)	4 (0.6%)	0	0	4 (0.3%)
Vasculitis	1 (0.1%)	2 (0.1%)	0	0	2 (0.1%)
Aortic Dissection	0	1 (0.1%)	0	0	1 (0.1%)
Hypertension	0	1 (0.1%)	0	0	1 (0.1%)

Adapted Sponsor's Table T79; Appendix 15 of the Summary of Clinical Safety Appendices.

AEs of Special Interest

Neuropsychiatric Adverse Events

Neuropsychiatric manifestations are a not uncommon complication of SLE, although the actual incidence of neuropsychiatric involvement appears to range widely depending on the population studied and the specific manifestation in question. Some sort of cognitive dysfunction is reported in the majority of patients (from 55% to 80%). Headache (24 to 72%) and mood disorders (14 to 57%) are also commonly reported. Depression and anxiety are common in SLE patients and have been reported to occur in 24 to 57% of SLE patients. Frank psychosis is relatively uncommon (up to 8% of patients).[7] Not unexpectedly, these adverse events have been reported in the belimumab SLE clinical development program; however once again, there was a numerical imbalance against belimumab, with more belimumab-treated patients reporting neurologic and psychiatric adverse events, SAEs, and suicides. Ascertaining the role of belimumab in this imbalance is again difficult, as patients were exposed to placebo-treatment for shorter durations and there was unequal randomization. However a promoting or permissive role of belimumab cannot be ruled out.

Narratives on Completed Suicides

1. Study LBSL02: Subject US034-002 was a 43-year-old white female with SLE. She received 2 doses of belimumab 1.0 mg/kg IV, on 23Oct03 and 07Nov03. Medical history included peptic ulcer, candidiasis, Raynaud's phenomenon, ileus, cutaneous vasculitis, uterine hemorrhage, pelvic pain, migraine, uterine leiomyoma, hemangioma of liver, tremor, nausea, nervous system disorder, hepatic cyst, hypokalemia, tinnitus, diplopia, reduced visual acuity, vertigo, gastroesophageal reflux disease, pyrexia, dehydration, anorexia, joint dislocation, connective tissue disorder, ovarian cyst, tobacco abuse, family stress, fractured coccyx, pelvic fracture, photosensitivity reaction, mouth ulceration, and stomatitis. Past medical and surgical procedures included abdominal hysterectomy, bilateral salpingo-oophorectomy, myomectomy, appendectomy, tonsillectomy and adenoidectomy. Ongoing medical conditions included fibromyalgia, osteoporosis, chronic sinusitis, hypertension, esophageal dyskinesia, depression, chronic fatigue syndrome, aptyalism, synovitis, insomnia, Sjogren's syndrome, intervertebral disc degeneration, contusion, amnesia, anxiety, intervertebral disc protrusion, arthritis, alopecia, and cerebral disorder. The screening physical examination on 01Oct03 revealed malar facial rash, thin hair, discoid patches on the arms, and synovitis of both hands. Concomitant medications included prednisone, citalopram, acetaminophen with hydrocodone, dextroamphetamine, carisoprodol, diazepam, metoclopramide, sucralfate, rabeprazole, propanolol, alendronate, celecoxib, and esomeprazole. On 27Nov03, the subject was considered to have worsening depression and committed suicide by a self-inflicted gunshot. No action was taken with regard to the study agent prior to the suicide.

[7] Hanly, Rheum Dis Clin N Am (2005) 31:273-298

2. Study 1057: Subject KR008-001 was a 23-year-old Asian female with SLE. She received her 1st dose of 10.0 mg/kg belimumab on 07Jan08 and received 11 doses. The subject discontinued belimumab on 05Oct08 because of this SAE; her last dose was on 22Sep08. Medical history included autoimmune thyroiditis, hepatitis (drug-induced), bronchitis, cystitis, herpes zoster, upper respiratory tract infection, depressed mood, and psychotic disorder due to general medical condition. Ongoing conditions included, drug hypersensitivity (penicillin and cephalosporins), and osteopenia. Concomitant medications included hydroxychloroquine, levothyroxine, acetylsalicylic acid, calcium carbonate, rebamipide, azathioprine, meloxicam, and methylprednisolone. On 05Oct08, 13 days after her 11th dose of belimumab, the subject committed suicide. Her condition was improving during the trial and her steroid dose had been tapered. When she missed her Week 40 visit, the study coordinator contacted the subject's family. The subject's mother informed the coordinator that the subject had committed suicide on 05Oct08 because of a conflict with her father. The subject did not have any mental illness as diagnosed by a psychiatrist; however, she had a period of a depressive mood in 2006. She had not been in a depressive state during the period that the suicide occurred. An autopsy was not performed.

3. Study LBSL99 (open-label extension of LBSL02): Subject US023-005 was a 65-year-old white female with SLE. She received her 1st dose of 10.0 mg/kg belimumab on 15Mar04 and completed both the 52-week treatment phase and the 24-week extension phase at that dosage. She continued to receive 10.0 mg/kg belimumab in LBSL99 (starting on 27Sep05). The subject's last dose of belimumab was on 21Mar06. Medical history included SLE-related conditions as well as hysterectomy and ruptured cerebral aneurysm with intra-cerebral aneurysm operation. Ongoing conditions included SLE-related conditions as well as seasonal allergies, hypertension, fibromyalgia, osteoarthritis, and insomnia. Concomitant medications included hydroxychloroquine, valsartan, hydrochlorothiazide, celecoxib, oxycodone, cyclobenzaprine, acetaminophen/codeine, and trazodone. On 13Apr06, 23 days after her 27th dose of belimumab (6th in LBSL99), the subject voiced complaints of "facial butterfly rash" to her spouse. She expressed fear that her SLE symptoms, which had been well controlled, were returning. In the morning of 15Apr06, the subject was found dead in bed. It initially appeared that she had taken all of her remaining anti-hypertensive medications. The site confirmed that the subject had no history of depression and no ongoing AEs. The subject was scheduled to receive her next dose of belimumab on 17Apr06. An autopsy report revealed that the subject was found with superficial cuts to the wrists and empty pill bottles. Her death was ascribed to oxycodone and alcohol intoxication.

Narratives on Suicide Attempts/Ideation

1. Study LBSL99: Subject US006-0008 is a 44-year-old female with systemic lupus erythematosus (SLE) who participated in Study LBSL99. The subject received her first dose of belimumab (1 mg/kg) on 27Jul04 in LBSL02, her first dose of belimumab (10 mg/kg) in the extension phase on 30Aug05, and her first dose of belimumab in LBSL99 on 07Feb06. Medical history is significant for depression, hypertension, obesity, and smoking. No previous psychiatric outpatient or inpatient hospitalizations. Concomitant

medications included citalapram hydrobromide, enalapril, hydrochlorothiazide, ranitidine, albuterol inhaler and hydroxyzine.

On 26Dec08, 21 days after her most recent dose of belimumab, the subject's husband found her sleepy and unresponsive and called the paramedics. She was transported via ambulance to the local hospital. Upon arrival, she was unresponsive and an ammonia capsule to the left nare resulted in a combative response. Her blood pressure was 145/87 mmHg, respirations 20 per minute, heart rate (HR) 109 beats per minute (bpm), temperature 98 degrees Fahrenheit, and oxygen saturation 94%. During her examination, she was anxious and uncooperative, but otherwise her exam was unremarkable. She reportedly took a drug overdose while intoxicated and was subsequently admitted for suicide gesture. Her hematology and chemistry laboratory results were normal except for potassium 3.5 mmol/L. Urinalysis and urine drug screen were normal. Her Tylenol level was normal at 12 and alcohol level was 68 mg/dL. A CT scan revealed no acute concerns. Arterial blood gas showed a pCO2 of 50. She was transferred to another hospital for psychiatric follow-up. The subject reported being lonely, discouraged, and upset with her sister. In addition, she reported stress secondary to family problems. She did not seek out help, but started drinking alcohol (unknown type) and took some pills (not identified and amount not provided by subject). She reported her plan was to hurt herself, although she was vague about a suicidal attempt. She reported not being suicidal, just reaching out for help. She had no delusions and repeatedly denied plans to kill herself. She was not considered psychotic. The evaluation indicated she had partial insight and questionable judgment when she is under the influence of alcohol. No gross abnormality was noted for short and long term memory. No action was taken with regard to belimumab.

2. Subject US003-0013 in ongoing long-term extension study LBSL99, receiving 10 mg/kg belimumab, reported depression and suicide attempt on 11 Jun 2009, 1364 days after first dose of belimumab. No further details provided.

3. One case of suicidal ideation reported in 1/79 (1.3%) subjects in the 4 mg/kg group of Study LBSL02. No further details were provided.

4. One case of "intentional self-injury" was reported in the placebo group of Study 1057: Subject IN004-010 was a 20-year-old Asian female with SLE. She received her 1st dose of placebo on 31Mar08, her last dose on 03Mar09, and she received 13 doses. No medical history was reported. Ongoing conditions included gastritis, vomiting, and depression. Concomitant medications included acetylsalicylic acid, calcium/cholecalciferol, folic acid, methotrexate, fluoxetine, paracetamol, octinoxate/arobenzone/oxybenzone, etoricoxib, nortriptyline, multivitamins, pantoprazole, and prednisolone.

For a few weeks prior to 16Jul08, the subject had been experiencing increased anger and outbursts. On 16Jul08, 21 days after her 5th dose of placebo, after being questioned and scolded by her father for poor performance on exams, the subject consumed 10 to 15 mL of phenyl with the intention of self harm. She was admitted to a local hospital on 16Jul08 and managed conservatively until discharge on 18Jul08. On 21Jul08, she was evaluated

by psychiatrists and on 22Jul08 she was hospitalized for treatment of adjustment disorder, personality disorder, and intentional self injury. Laboratory tests of cerebrospinal fluid an MRI of the brain, and cerebrospinal fluid analysis results were all normal. She was treated with alprazolam and fluoxetine. The subject was discharged on 02Aug08. No action was taken with regard to placebo.

Neurologic and Psychiatric Adverse Events

Neurologic and Psychiatric SAE and common AE are listed in Tables 44 and 45 below:

Table 44: Neurologic and Psychiatric SAE in Studies LBSL02, 1056 and 1057

Neurologic and Psychiatric Serious Adverse Events in Studies LBSL02, C1056, and C1057				
	Placebo n = 675	1 mg/kg n = 673	4 mg/kg n = 111	10 mg/kg n = 674
Nervous System Disorders	**8 (1.2)**	**10 (1.5)**	**1 (0.9)**	**16 (2.4)**
Exposure-Adjusted Incidence[1] per 100 pt-yrs	**1.2**	**Combined: 1.8**		
Headache	1 (0.1)	1 (0.1)		4 (0.6)
TIA		2 (0.3)	1 (0.9)	1 (0.1)
Convulsion	1 (0.1)	2 (0.3)		2 (0.3)
Lupus encephalitis	1 (0.1)			1 (0.1)
Neuropsychiatric lupus				2 (0.3)
Syncope	1 (0.1)			1 (0.1)
Amnesia				1 (0.1)
Cauda equina syndrome				1 (0.1)
Intracranial hemorrhage	3 (0.4)			
Cerebral infarction	1 (0.1)			
Dizziness				1 (0.1)
Hypoesthesia				1 (0.1)
Intracranial hypotension				1 (0.1)
Ischemic stroke		1 (0.1)		
Mononeuropathy multiplex		1 (0.1)		
Myasthenia gravis				1 (0.1)
Transverse myelitis		1 (0.1)		
Neuritis		1 (0.1)		
Occipital neuralgia				1 (0.1)
Paresthesia		1 (0.1)		
Peripheral sensory neuropathy		1 (0.1)		
Reversible posterior leukoencephalopathy	1 (0.1)			
Cerebral vasculitis	1 (0.1)			
Psychiatric Disorders	**3 (0.4)**	**4 (0.6)**	**0**	**8 (1.2)**
Exposure-Adjusted Incidence[1] per 100 pt-yrs	**0.4**	**Combined: 0.8**		
Depression	1 (0.1)	3 (0.4)		3 (0.4)
Completed suicide		1 (0.1)		1 (0.1)
Mania		1 (0.1)		1 (0.1)
Panic attack	1 (0.1)			1 (0.1)
Adjustment disorder	1 (0.1)			
Delirium				1 (0.1)
Drug Abuse				1 (0.1)
Insomnia		1 (0.1)		
Intentional self-injury	1 (0.1)			
Personality disorder	1 (0.1)			

Source: Table T64 of Summary of Clinical Safety Appendices

[1]Exposure is 672.3 subject-years for placebo and 1472.9 subject-years for combined belimumab groups

Table 45: Neurologic and Psychiatric Common Adverse Events in Studies LBSL02, 1056 and 1057

Neurologic and Psychiatric Common Adverse Events of Higher Frequency (and occurring more than once) in the Belimumab Treatment Groups of Studies LBSL02, C1056, and C1057				
	Placebo n = 675	1 mg/kg n = 673	4 mg/kg n = 111	10 mg/kg n = 674
Nervous System Disorders	**241 (35.7)**	**231 (34.3)**	**58 (52.3)**	**249 (36.9)**
Exposure-Adjusted Incidence[1] per 100 pt-yrs	**35.8**	**Combined: 36.5**		
Migraine	27 (4.0)	24 (3.6)	6.5 (5.4)	35 (5.2)
Paresthesia	9 (1.3)	24 (3.6)	3 (2.7)	8 (1.2)
Hypoesthesia	10 (1.5)	12 (1.8)	5 (4.5)	14 (2.1)
Convulsions/seizures	3 (0.4)	8 (1.2)	1 (0.9)	6 (0.9)
Amnesia	1 (0.1)	1 (0.1)		3 (0.4)
Loss of consciousness	2 (0.3)	3 (0.4)		
Ataxia		1 (0.1)		2 (0.3)
Cervicobrachial syndrome		3 (0.4)		
Myoclonus		1 (0.1)		2 (0.3)
Poor quality sleep	1 (0.1)			2 (0.3)
Trigeminal neuralgia	1 (0.1)	2 (0.3)		
Visual field defect	1 (0.1)			2 (0.3)
Balance disorder			1 (0.9)	1 (0.1)
Depressed level of consciousness				2 (0.3)
Disturbance in attention			1 (0.9)	1 (0.1)
Hypogeusia		1 (0.1)		1 (0.1)
Intercostal neuralgia		1 (0.1)		1 (0.1)
Monoparesis		2 (0.3)		
Myelopathy		2 (0.3)		
Nerve compression		1 (0.1)		1 (0.1)
Neuropsychiatric lupus				2 (0.3)
Radiculopathy		1 (0.1)		1 (0.1)
Psychiatric Disorders	**82 (12.1)**	**103 (15.3)**	**25 (22.5)**	**100 (14.8)**
Exposure-Adjusted Incidence[1] per 100 pt-yrs	**12.2**	**Combined: 15.5**		
Insomnia/sleep disorder	36 (5.3)	38 (5.6)	5 (4.5)	46 (6.8)
Depression/Depressed mood	30 (4.4)	43 (6.4)	12 (10.8)	36 (5.3)
Anxiety/Anxiety disorder/Nervousness	21 (3.1)	35 (5.2)	8 (7.2)	17 (2.5)
Panic attack	1 (0.1)	1 (0.1)	1 (0.9)	2 (0.3)
Mood alteration		1 (0.1)		3 (0.4)
Mental disorder due to medical condition			3 (2.7)	
Completed suicide		1 (0.1)		1 (0.1)
Suicidal ideation			1 (0.9)	
Intentional self-injury	1 (0.1)			
Loss of libido		1 (0.1)		1 (0.1)
Mania		1 (0.1)		1 (0.1)
Mood swings/lability				3 (0.4)

Source: Table T19 of Summary of Clinical Safety Appendices

[1]Exposure is 672.3 subject-years for placebo and 1472.9 subject-years for combined belimumab groups

As noted in tables 44 and 45 above, there is a consistent overall numeric and exposure-adjusted imbalance against belimumab in reported neurologic and psychiatric serious AE and common AE.

Infusion Reactions, Hypersensitivity, and Anaphylaxis

Because belimumab is a protein for infusion that contains foreign sequences, a certain level of infusion reactions, hypersensitivity, and anaphylaxis would be expected. Describing these events is difficult to do with accuracy, and no consistent methodology

was used in the belimumab clinical development program for capturing and classifying these events. FDA asked the Applicant to retrospectively assess adverse events to determine whether they met clinical criteria for diagnosing anaphylaxis, as agreed upon at the Second Symposium on the Definition and Management of Anaphylaxis sponsored by the National Institute of Allergy and Infectious Disease (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN). These criteria are summarized in Table 46, below.

Table 46 Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) *AND AT LEAST ONE OF THE FOLLOWING* a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure *to a likely allergen for that patient* (minutes to several hours): a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula) b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence) d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to *known allergen for that patient* (minutes to several hours): a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP* b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

PEF, Peak expiratory flow; *BP*, blood pressure.
*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

Source: Sampson et al., J Allergy Clin Immunol, 2006, 117(2) :391-397

Because of the overlap in symptoms with infusion reactions, hypersensitivity reactions, and anaphylaxis, it is difficult to ensure that adverse events were adequately captured and classified. The data for belimumab are summarized in Table 47, below. These data raise some concerns, as follows:

- The placebo rate of events seems unusually high, both for infusion reactions and more specific, suspected hypersensitivity events. It does not appear likely that this is due to the placebo formulation, and it seems unlikely that the few patients who incorrectly received active treatment account for this observation, unless additional placebo patients were unknowingly given active treatment.
- Based on review of the line listings, the estimated rate of anaphylaxis is 0.6% for belimumab vs 0.4% for placebo. This rate seems low compared to other approved monoclonal antibodies. There may be additional cases of anaphylaxis in the belimumab program when the NIAID/FAAN clinical criteria are correctly applied. For example, there were several cases of AEs coded as infusion reactions, but the case report forms noted additional findings such as urticaria and shortness of breath. But there were others that just said "infusion related reaction" or "infusion related reaction – allergic reaction," coded as severe, and the patient was discontinued.
- Patients inconsistently received prophylaxis for infusion reactions, which included antihistamines and corticosteroids, at the discretion of the investigator. This may have blunted or obscured hypersensitivity responses.

Table 47: Summary of Infusion Reactions, Hypersensitivity, and Anaphylaxis

Primary safety population (IV SLE CRD)	Belilumab 1 mg/kg N=673 N (%)	Belilumab 4 mg/kg N=111 N (%)	Belilumab 10 mg/kg N=674 N (%)	Placebo N=675 N (%)
BLA Original Analysis				
All infusion and hypersensitivity reactions (HGS definition)			251, 17% (all belimumab groups doses)	99 (15)
All hypersensitivity reactions occurring on infusion days (HGS definition)	3 (0.4)	1 (1.8)	3 (0.4)	1 (0.1)
"Potential hypersensitivity" (per HGS interpretation of Sampson criteria))	2 (0.3)	3 (2.7)	9 (1.3)	7 (1.0)
FDA-Requested Additional Analyses				
Leading to discontinuation/interruption (regardless of day of occurrence)				
Hypersensitivity reactions (HGS definition)	5 (0.7)	1 (0.9)	3 (0.4)	1 (0.1)
Infusion reactions and hypersensitivity rxns combined	28 (4.2)	6 (5.4)	22 (3.3)	23 (3.4)
Serious and/or severe				
Serious and/or severe Infusion and hypersensitivity rxns (HGS definition)	40 (5.9)	10 (9.0)	46 (6.8)	37 (5.5)
FDA terms				
All hypersensitivity reactions occurring on day of infusion	91 (13.5)	27 (24.3)	73 (10.8)	76 (11.3)
Severe and/or serious reactions	6 (0.9)	-	6 (0.9)	2 (0.3)
Anaphylaxis (per FDA analysis)*	5 (0.7)	1 (0.9)	3 (0.4)	3 (0.4)

*Based on FDA review of line listings, the estimated anaphylaxis rate is 0.6% for the combined belimumab groups vs. 0.4% for placebo. See appendix for cases. Table courtesy of Dr. Susan Limb.

Common Adverse Events

Most patients (>92%) experienced an adverse event during the controlled IV SLE trials. Table 48 lists the frequency of the adverse events observed in these studies by system organ class and treatment group. Infections and Infestations, Musculoskeletal and Connective Tissue Disorders, Gastrointestinal Disorders, Skin and Subcutaneous Tissue Disorders and Nervous System Disorders were the most common types of adverse events observed. Overall, the types and incidences of common adverse events were consistent with what would be expected for patients with active SLE who had been exposed to immunosuppressive therapies. The incidences for these adverse event categories were similar for the placebo and belimumab 1 mg/kg and 10 mg/kg groups; however, they were frequently higher in the belimumab 4 mg/kg group, which was much smaller in size (thus small numeric changes resulted in larger proportional changes).

Table 48: Common Adverse Events in Studies LBSL02, 1056, and 1057

MedDRA System Organ Class	Placebo N=675	Belimumab 1mg/kg N=673	Belimumab 4 mg/kg N=111	Belimumab 10mg/kg N=674	Total Belimumab N= 1458
Number of Subjects with a ≥ 1AE:	**624 (92%)**	**626 (93%)**	**107 (96%)**	**625 (93%)**	**1358 (93%)**
Blood and Lymphatic System Dis.	90 (13%)	85 (13%)	21 (19%)	87 (13%)	193 (13%)
Cardiac Disorders	45 (7%)	44 (7%)	14 (13%)	55 (8%)	113 (8%)
Congenital, Familial and Genetic Disorders	1 (0.1%)	1 (0.1%)	1 (1%)	2 (0.3%)	4 (0.3%)
Ear and Labyrinth Disorders	33 (5%)	45 (7%)	9 (8%)	28 (4%)	82 (6%)
Endocrine Disorders	8 (1%)	13 (2%)	5 (5%)	11 (2%)	29 (6%)
Eye Disorders	59 (9%)	70 (10%)	15 (14%)	73 (11%)	158 (11%)
Gastrointestinal Disorders	268 (40%)	261 (39%)	61 (55%)	288 (32%)	610 (42%)
General Disorders and Administrative Site Conditions	206 (31%)	193 (29%)	63 (57%)	215 (32%)	471 (32 %)
Hepatobiliary Disorders	18 (3%)	16 (2%)	6 (5%)	15 (2%)	37 (3%)
Immune System Disorders	21 (3%)	30 (5%)	5 (55)	19 (3%)	54 (4%)
Infections and Infestations	450 (67%)	478 (71%)	88 (79%)	471 (70%)	1037 (71%)
Injury, Poisoning and Procedural Complications	114 (17%)	112 (17%)	37 (33%)	123 (18%)	272 (19%)
Investigations	103 (15%)	93 (14%)	41 (37%)	95 (14%)	229 (16%)
Metabolism and Nutrition Disorders	67 (10%)	62 (9%)	18 (16%)	78 (12%)	158 (11%)
Musculoskeletal and Connective Tissue Disorder	310 (46%)	286 (43%)	72 (65%)	297 (44%)	655 (45%)
Neoplasms Benign, Malignant and Unspecified (incl. cysts/polyps)	25 (4%)	24 (4%)	3 (3%)	18 (3%)	45 (35%)
Nervous System Disorders	241 (36%)	231 (34%)	58 (52%)	249 (37%)	538 (37%)
Pregnancy, Puerperium and Perinatal Conditions	4 (0.6%)	3 (0.4%)	0	5 (1%)	8 (0.6%)
Psychiatric Disorders	82 (12%)	103 (15%)	25 (23%)	100 (15%)	228 (16%)
Renal and Urinary Disorders	82 (12%)	63 (9%)	15 (14%)	73 (11%)	151 (10%)
Reproductive System and Breast Disorders	68 (10%)	73 (11%)	12 (11%)	69 (10%)	154 (11%)
Respiratory, Thoracic and Mediastinal Disorders	179 (27%)	176 (26%)	39 (35%)	159 (24%)	374 (26%)
Skin and Subcutaneous Tissue Disorders	235 (35%)	251 (37%)	65 (59%)	233 (35%)	549 (38%)
Social Circumstances	0	2 (0.3%)	0	0	2 (0.1%)
Surgical and Medical Procedures	13 (2%)	9 (1%)	10 (9%)	14 (2%)	33 (2%)
Vascular Disorders	103 (15%)	94 (14%)	23 (21%)	95 (14%)	212 (15%)

Adapted Sponsor's Table T17; Appendix 15 of the Summary of Clinical Safety.

Table 49 lists common adverse event preferred terms reported by 5% or more patients in any treatment group during the controlled IV SLE trials. The adverse events most commonly reported by belimumab treated patients were: headache, upper respiratory tract infection, arthralgia, nausea, urinary tract infection, and diarrhea. Overall, the incidences for individual adverse events were similar across the placebo and belimumab 1 mg/kg and 10 mg/kg treatment groups but were again frequently higher in the 4 mg/kg group. No dose-dependent phenomena are apparent on the basis of these data.

Table 49: Common AEs Occurring at >5% Frequency in Any Treatment Group in Studies LBSL02, 1056, and 1057, by Preferred Term

MedDRA System Organ Class/Preferred Term	Placebo N=675	Belimumab 1mg/kg N=673	Belimumab 4 mg/kg N=111	Belimumab 10mg/kg N=674	Total Belimumab N= 1458
Headache	140 (21%)	138 (21%)	30 (27%)	142 (21%)	310 (21%)
Upper Respiratory Tract Infection	130 (19%)	128 (19%)	36 (32%)	118 (18%)	282 (19%)
Arthralgia	112 (17%)	100 (15%)	32 (29%)	109 (16%)	241 (17%)
Nausea	82 (12%)	88 (13%)	22 (20%)	99 (15%)	209 (14%)
Urinary Tract Infection	82 (12%)	92 (14%)	19 (17%)	87 (13%)	198 (14%)
Diarrhea	62 (9%)	81 (12%)	23 (21%)	80 (12%)	184 (13%)
Fatigue	70 (10%)	71 (11%)	33 (30%)	66 (10%)	170 (12%)
Back Pain	62 (9%)	64 (10%)	15 (14%)	60 (9%)	139 (10%)
Edema Peripheral	54 (8%)	62 (9%)	19 (17%)	56 (8%)	137 (9%)
Pyrexia	52 (8%)	52 (8%)	17 (15%)	65 (10%)	134 (9%)
Nasopharyngitis	48 (7%)	57 (9%)	2 (2%)	61 (9%)	120 (8%)
Cough	49 (7%)	54 (8%)	8 (7%)	52 (8%)	114 (8%)
Vomiting	44 (7%)	49 (7%)	15 (14%)	46 (7%)	110 (8%)
Sinusitis	54 (8%)	34 (5%)	15 (14%)	49 (7%)	98 (8%)
Bronchitis	35 (5%)	43 (6%)	12 (11%)	60 (9%)	115 (8%)
Myalgia	47 (7%)	46 (7%)	10 (9%)	46 (7%)	102 (7%)
Influenza	42 (6%)	47 (7%)	11 (10%)	47 (7%)	105 (7%)
Hypertension	55 (8%)	42 (6%)	5 (5%)	43 (6%)	90 (6%)
Arthritis	41 (6%)	35 (5%)	21 (19%)	40 (6%)	96 (7%)
Rash	35 (5%)	46 (7%)	17 (15%)	35 (5%)	98 (7%)
Dizziness	42 (6%)	38 (6%)	12 (11%)	37 (6%)	87 (6%)
Insomnia	36 (5%)	37 (6%)	5 (5%)	44 (7%)	86 (6%)
Pain in Extremity	27 (4%)	35 (5%)	13 (12%)	40 (6%)	88 (6%)
Depression	25 (4%)	41 (6%)	12 (11%)	35 (5%)	88 (6%)
Mouth Ulceration	35 (5%)	23 (3%)	12 (11%)	36 (5%)	71 (5%)
Abdominal Pain	35 95%)	33 (5%)	5 (5%)	32 (5%)	70 (5%)
Gastroenteritis	32 (5%)	36 (5%)	3 (3%)	25 (4%)	64 (4%)
Anemia	31 (5%)	27 (4%)	7 (6%)	30 (5%)	64 (4%)
Alopecia	33 (5%)	24 (4%)	9 (8%)	26 (4%)	59 (45)
Non-Cardiac Chest Pain	34 (5%)	23 (3%)	6 (5%)	28 (4%)	57 (45)
Migraine	27 (4%)	23 (3%)	6 (5%)	34 (5%)	63 (4%)
Weight Increased	24 (4%)	24 (4%)	8 (7%)	27 (45)	59 (4%)
Dyspnea	31 (5%)	20 (3%)	8 (7%)	15 (2%)	43 (3%)
Viral Upper Respiratory Tract Infection	21 (3%)	22 (3%)	8 (7%)	21 (3%)	51 (3%)
Musculoskeletal Pain	22 (3%)	18 (3%)	11 (10%)	20 (3%)	49 (3%)
Anxiety	17 (3%)	30 (5%)	7 (6%)	15 (2%)	52 (4%)
Vulvovaginal Mycotic Infection	22 (3%)	20 (3%)	8 (7%)	18 (3%)	46 (3%)
Leukopenia	15 (2%)	20 (3%)	6 (5%)	25 (4%)	51 (3%)
Joint Swelling	18 (3%)	17 (3%)	11 (10%)	18 (3%)	46 (3%)
Contusion	17 (3%)	18 (3%)	7 (6%)	19 (3%)	44 (3%)
Rash Maculo-Papular	25 (4%)	15 (2%)	6 (5%)	14 (2%)	35 (2%)
Musculoskeletal Chest Pain	15 (2%)	19 (3%)	6 (5%)	15 (2%)	40 (3%)
Proteinuria	21 (3%)	11 (2%)	7 (6%)	15 (2%)	33 (2%)
Urticaria	15 (2%)	14 (2%)	7 (6%)	15 (2%)	36 (2%)
Erythema	12 (2%)	19 (3%)	10 (9%)	8 (1%)	37 (3%)
Pain	6 (1%)	5 (1%)	6 (5%)	13 (2%)	24 (2%)
Infusion Site Extravasation	9 (1%)	6 (1%)	12 (11%)	2 (0%)	20 (1%)
Synovitis	5 (1%)	5 (1%)	6 (5%)	10 (2%)	21 (1%)
Creatinine Renal Clearance Decreased	4 (1%)	5 (1%)	8 (7%)	5 (1%)	18 (1%)
Viral Infection	4 (1%)	5 (1%)	7 (6%)	1 (0%)	13 (1%)

Adapted Sponsor's Table T21; Appendix 15 of the Summary of Clinical Safety.

Laboratory Findings

As shown in Table 50 below, there does appear to be a generally dose-related trend toward a higher proportion of patients experiencing low immunoglobulin levels of each isotype with exposure to higher dose regimens of belimumab. As might be expected, the largest impact appeared to be on IgM levels, which have the ability to change the most acutely. With increasing duration of exposure to belimumab, the proportion of patients with IgG less than the lower limit of normal increased over time from 8% to 14% (as per section 2.7.4.3.6.1.2 and the LBSL99 clinical study report). The proportion of patients with IgM less than the lower limit of normal increased from 33% to 63% over time and levels of IgA were stable. As per the applicant, there was not a corresponding increase in infections or serious infections.

B cell numbers were only evaluated in Study C1056. At Week 24, the median percent reduction in CD19+ B cells was 29-32% with belimumab treatment, while the reduction in the placebo group was approximately 3%; at Week 52 the median percent reduction with belimumab was 48% compared with 10% with placebo; and at Week 76 the median percent reduction with belimumab was 56-58% compared with 3% with placebo. Given that rituximab is associated with an almost complete B-cell depletion, this degree of B-cell depletion would not be especially concerning. However there did appear to be an increased risk of infections with belimumab treatment and low immunoglobulins and B cell levels almost certainly contribute to this.

Table 50: Immunoglobin Shifts from Baseline In Studies LBSL02, C1056, and C1057

Immunoglobulin Shifts from Baseline in Studies LBSL02, C1056, and C1057				
	Placebo n = 675	1 mg/kg n = 673	4 mg/kg n = 111	10 mg/kg n = 674
IgA				
Shift from Normal/High to Low, n (%)	8 (1.2)	13 (2.0)	4 (3.7)	17 (2.6)
Shift from Normal/High to High, n (%)	23 (3.5)	8 (1.2)	2 (1.9)	5 (0.8)
IgG				
Shift from Normal/High to Low, n (%)	19 (2.9)	32 (4.8)	5 (4.6)	42 (6.3)
Shift from Normal/High to High, n (%)	72 (10.8)	31 (4.7)	4 (3.7)	29 (4.4)
IgM				
Shift from Normal/High to Low, n (%)	39 (6.0)	110 (16.9)	23 (21.3)	122 (18.5)
Shift from Normal/High to High, n (%)	11 (1.7)	2 (0.3)	2 (1.9)	3 (0.5)

Source: Table T210 in Summary of Clinical Safety Appendices

Immunogenicity

Immunogenicity assay results for the two pivotal studies are summarized in Table 51 below. The highest rate of immunogenicity appears to be associated with the lower (1 mg/kg) dose of belimumab, which may be due to less immunosuppression at this dose. The apparently higher rate of persistent immunogenicity with exposure to placebo raises questions regarding how many placebo-treated patients were errantly exposed to belimumab. The dose proposed for marketing, 10 mg/kg, is associated with the lowest immunogenic response. There did not appear to be an association of anti-product

antibody positivity and risk for adverse events, but it is difficult to draw definitive conclusions with so few patients being anti-product antibody positive.

Table 51: Immunogenicity Results in Studies C1056 and C1057

Immunogenicity Results in Studies C1056 and C1057			
	Placebo	**1 mg/kg**	**10 mg/kg**
Number Enrolled	**n = 675**	**n = 673**	**n = 674**
Number Tested	**n = 562**	**n = 559**	**n = 563**
Persistently Positive[1]	**10 (1.8)**	**27 (4.8)**	**4 (0.7)**
NA/Negative to positive	10 (1.8)	26 (4.7)	4 (0.7)
Positive to positive		1 (0.2)	
Any positive neutralizing antibody assay[2]	7/10	3/11	0/1
Assay Positive Patients with ≥1 AE	1 (10.0)	2 (7.4)	1 (25)
Transiently Positive[3]	**1 (0.2)**	**46 (8.2)**	**1 (0.2)**
NA/Negative to positive	1 (0.2)	44 (7.9)	1 (0.2)
Positive to negative		2 (0.4)	
Any positive neutralizing antibody assay[2]		1/11	
Negative throughout	**551 (98.0)**	**486 (86.9)**	**558 (99.1)**

Source: Table T216 in Summary of Clinical Safety Appendices

[1]Persistently positive is a positive result at 2 or more assessments or the final assessment

[2]Transiently positive is a positive results at only 1 assessment and negative at the final

[3]Neutralizing any time post-baseline among subjects with neutralization assay results

Safety Conclusions

Treatment with belimumab appeared to be associated with an increase in death, serious adverse events, infections and serious infections, and neurologic and psychiatric adverse events/serious adverse events, including 3 suicides in belimumab-treated patients through the data cut-offs of the BLA submission. This imbalance holds true even when the incidence of these adverse events is adjusted for exposure. In some cases, the magnitude of the difference between the belimumab and placebo treatment group in the trials was relatively large, such as the almost 2-fold increase in exposure-adjusted incidence of mortality for belimumab-treated patients.

Conclusion

In two randomized, controlled trials, belimumab demonstrated a statistically significant difference in the proportion of responders as defined by the primary endpoint of SRI in the treatment of autoantibody positive SLE. However, the results in Study 1056 are less robust, and for both studies data from other endpoints and subgroup analyses were not consistently supportive. In light of this somewhat marginal efficacy, the relative safety profile of the product must be weighed. Increased risk of serious infection is almost a given with biologic immunosuppressives, so the risk of infection with belimumab is expected. Somewhat unexpectedly, though perhaps not unusual given the underlying

characteristics of the SLE population, there may be an increase in the risk for neuropsychiatric adverse events with belimumab treatment.

Clearly there is a need for effective therapies in SLE. However whether belimumab's benefits sufficiently outweigh its risks is the crux of the issue. Given that flares and steroid reduction may not be impacted, is a reduction of 4 points in the SELENA-SLEDAI (the main component driving Study 1056's efficacy result) clinically meaningful? If belimumab only has a modest effect for some patients and manifestations, is a possible increased risk of death, infection, or neuropsychiatric adverse effects worth the potential benefit?

Additionally, patients with serious SLE manifestations, such as renal and CNS lupus, were excluded from the studies. If belimumab is not effective for serious SLE manifestations, then it is likely that more potent immunosuppressives, including possibly other biologics, will be needed; the safety of combining of combining those immunosuppressives with belimumab will not have been adequately evaluated.

These are the dilemmas posed by the BLA for belimumab in SLE. FDA greatly appreciates the Advisory Committee's consideration and input on these weighty issues.

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Appendices

Anaphylaxis cases

C1057 (placebo)

- CO007-000005: dyspnea, flushing, pruritus, rash (11/27/07, #6)

C1056 (placebo)

- none

C1057 (1 mg/kg)

- CO007-000026: dizziness, flushing (8/27/08, infusion #7)
- CO008-000011: cough, pharyngeal itching (4/8/08, #3)
- IN005-000027: anaphylaxis (11/5/07, #1, discontinued)
- TW004-000008: angioedema and anaphylaxis (4/11/08, #1, coded life threatening, discontinued)

C1057 (10 mg/kg)

- BR006-000003: dyspnea, eyelid edema, erythematous rash on neck and face, pruritus, (3/24/08, #1, discontinued)
- IN005-000017: anaphylaxis, angioedema, hypotension, treated with chlorpheniramine, methylprednisolone, epinephrine, oxygen (10/15/07, #1, discontinued)

C1056 (10 mg/kg)

- US026-000009: "infusion reaction: rash, itching, chest tightness, lip edema" (11/20/07, #1, discontinued)

LBSL02 (placebo)

- US016-0000010: palpitations, light-headedness, shortness of breath, itching all over (2/19/04)
- US046-0000018: dyspnea, jaw pain, leg cramps, pruritus (10/15/04, discontinued)

LBSL02 (1 mg/kg)

- US031-000007: infusion reaction – dyspnea, facial flushing (6/10/05)

LBSL99 (long term extension)

4mg/kg, extension 4 mg/kg, LBSL99 10 mg/kg

- US008-000008: infusion related reaction – allergic reaction to study medication, shortness of breath, nausea/vomiting, swelling in mouth, tightness in chest, abdominal pain, lump in throat, difficulty breathing (8/30/06, discontinued)

Do not meet criteria but suspicious hypersensitivity event → discontinuation or interrupted (not counted in anaphylaxis rate calculation)

C1057, 10mg/kg

- PH002-000001: infusion related reaction – "study drug allergy," treated with diphenhydramine and hydrocortisone (12/20/07, #1, coded as severe, discontinued)
- IN005-000003: infusion related reaction – urticaria, treated with prednisolone, betamethasone, pheneramine (8/16/07, #1, coded as severe, discontinued)

C1056 10mg/kg

- US008-000003: infusion reaction, pre-treatment with benadryl and acetaminophen, additional treatment with Benadryl and albuterol nebs (11/28/07, #2, discontinued)
- CZ002-000005: "allergic reaction after infusion" (12/12/07, #2), no CRF
- NL001-000001: "infusion reaction allergic reaction after study medication blyss", treated with clemastine and hydrocortisone (11/29/07, #2, discontinued)

Other anaphylaxis (not counted in anaphylaxis rate calculation)
LBRA99 (RA study)
1 mg/kg, extension: 10 mg/kg, LBRA99: 10 mg/kg

- US027-000004: infusion related reaction – angioedema, non productive cough, pruritus (2/2/05, interrupted)
- uS040-000004: generalized edema, dyspnea (8/6/08) plus generalized pruritus reported 8/10/08
- US051-000001: non productive cough with study drug infusion, urticaria (1/21/05)
- US051-000004: nonproductive cough, tickle in throat (11/16/05)

Guidance for Industry

Systemic Lupus Erythematosus — Developing Medical Products for Treatment

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

June 2010
Clinical/Medical

Guidance for Industry

Systemic Lupus Erythematosus — Developing Medical Products for Treatment

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10903 New Hampshire Ave., Bldg. 51, rm. 2201
Silver Spring, MD 20993-0002
Tel: 301-796-3400; Fax: 301-847-8714; E-mail: druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

or

Office of Communication, Outreach, and Development, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448
Tel: 800-835-4709 or 301-827-1800; E-mail: ocod@fda.hhs.gov
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm

or

Office of Communication, Education, and Radiation Programs
Division of Small Manufacturers, International, and Consumer Assistance, HFZ-220
Center for Devices and Radiological Health
Food and Drug Administration
1350 Piccard Drive, Rockville, MD 20850-4307
DSMICA E-mail: dsmica@cdrh.fda.gov; DSMICA Fax: 301-443-8818
(Tel) Manufacturers Assistance: 800-638-2041 or 301-443-6597
(Tel) International Staff: 301-827-3993
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

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Clinical/Medical

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Contains Nonbinding Recommendations

Guidance for Industry[1] Systemic Lupus Erythematosus — Developing Medical Products for Treatment

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the clinical development of medical products (i.e., human drugs, therapeutic biological products, and medical devices) for the treatment of systemic lupus erythematosus (SLE). Specifically, this guidance addresses the Food and Drug Administration's (FDA's) current thinking regarding the overall development program and clinical trial designs, and provides specific information on trial design, trial duration, efficacy endpoints, and response criteria. This guidance is intended to serve as a focus for continued discussions among the FDA, medical industry, sponsors, academic community, and the public.[2] As the science of this indication evolves, this guidance may be revised.

This guidance applies to general information regarding medical product development for the treatment of SLE. Organ-specific forms of disease will be addressed in separate guidances.

This guidance does not contain discussion of the general issues of clinical trial design or statistical analysis. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical*

[1] This guidance has been prepared by the Systemic Lupus Erythematosus Working Group, which includes representatives from the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), the Center for Devices and Radiological Health (CDRH), and the Office of Critical Path Programs (OCPP) in the Office of the Commissioner (OC) at the Food and Drug Administration.

[2] In addition to consulting guidances, sponsors are encouraged to contact the relevant division to discuss specific issues that arise during the development of SLE medical products.

Trials.[3] This guidance focuses on specific medical product development and trial design issues that are unique to the study of SLE.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

SLE is a chronic disease characterized by protean manifestations, often with a waxing and waning course. In the past, a diagnosis of SLE often implied a decreased life span caused by internal organ system involvement or the toxic effects of therapy, but recent improvements in care have dramatically enhanced the survival of SLE patients. Nonetheless, increased mortality remains a major concern and current treatments for SLE remain inadequate.[4] Many patients have incompletely controlled disease, progression to end-stage organ involvement continues, and the therapies carry risks of debilitating side effects. Therefore, it is important to facilitate the development of medical products that have the potential to be more effective and/or less toxic.

III. DEVELOPMENT PROGRAM

A. General Considerations

1. Early Phase Clinical Development Considerations

Studies to identify an appropriate (safe and effective) dose are an important component of phase 2 development for human drugs and therapeutic biological products used to treat SLE. For additional information on the FDA's current thinking regarding exposure response or dose response, see the ICH guidance for industry *E4 Dose-Response Information to Support Drug Registration* and the guidances for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* and *Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications*.

We recommend that early studies evaluate concurrent use of a new medical product with commonly used standard therapies to obtain preliminary safety information on potential interactions with medical products used in standard-of-care regimens, although at this stage studies will not be powered to fully assess safety endpoints. As discussed in section III.B.8., Primary Efficacy Endpoints, early exploratory clinical studies can be used to gain experience

[3] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Guidances Web page at http://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[4] Ippolito, A and M Petri, 2008, An Update on Mortality in Systemic Lupus Erythematosus, Clin Exp Rheumatol, 26(5 Suppl 51):S72-9.

with a variety of standard clinical outcome measures, which may aid sponsors in determining which endpoints to pursue further in phase 3 trials.

Biomarker assays thought to reflect disease activity also can be helpful in identifying medical products likely to show a clinical benefit and in choosing doses and regimens. See section III.B.10., Other Endpoints, for additional information on the use of biomarkers in SLE clinical studies.

2. Efficacy Considerations

The evidence of effectiveness needed to support approval of medical products for SLE is similar to that for medical products for other indications. For human drugs and therapeutic biological products, at least two adequate and well-controlled trials generally are needed for approval. However, a single study can suffice under some circumstances(see the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products*). A single study can be sufficient, for example, if the medical product is being developed for the treatment of serious acute manifestations and the study shows: (1) robust evidence of efficacy with resolution of the serious acute manifestations; or (2) a decrease in mortality. For medical devices, one confirmatory clinical trial generally is sufficient.

B. Specific Efficacy Trial Considerations

1. Indication

The general indication of *treatment of systemic lupus erythematosus* will be granted for medical products if supported by sufficient evidence of effectiveness. In general, specific efficacy claims (e.g., reduction in disease activity), as discussed in section III.B.8., Primary Efficacy Endpoints, will not be included in the INDICATIONS AND USAGE section of labeling, but can be discussed in the CLINICAL STUDIES section if well-supported. If the medical product is studied only in a subset of the general SLE population, then the restricted population in which the medical product was studied would be reflected in labeling. For medical products that demonstrate a reduction in mortality in adequate and well-controlled trials, appropriate additional labeling reflecting that outcome would be included in the INDICATIONS AND USAGE section.

2. Study Design

a. Superiority trials

The preferred design for efficacy trials is a parallel, randomized, controlled superiority trial using placebo or active control. The placebo-controlled trial can compare the test medical product with no treatment, but more commonly adds the test medical product or placebo to standard therapy (add-on trial).

No patient enrolling in an SLE clinical trial should be denied standard therapy if doing so would lead to irreversible harm. To avoid denying patients standard of care, superiority trials of new therapies can use an add-on design, if the medical product is intended as adjunctive treatment, or

head-to-head comparisons with an alternative standard of care, if the medical product is intended for primary treatment. In a head-to-head comparison, it may be appropriate to include early escape provisions to an alternative standard-of-care regimen for patients who worsen during the study to ensure that no patient is denied potentially effective therapy.

One of the advantages to an add-on trial of this type is that it enables the evaluation of drug effects in the context of commonly used medical products in SLE. An example of an add-on design would be a trial of corticosteroids plus placebo compared to corticosteroids plus the new medical product. The protocol should specify the dose of corticosteroids patients will receive, taking into account the type and severity of the clinical manifestation. The protocol also should include provisions for tapering of corticosteroids during the trial if the manifestations improve.

b. Noninferiority trials

If superiority to a comparator is unlikely (e.g., because the new medical product is pharmacologically similar to a standard-of-care medical product) and an add-on study would be unlikely to succeed (again because the new and standard-of-care medical products are pharmacologically similar), sponsors might want to consider a noninferiority design to evaluate efficacy. However, this design would be difficult to support in this case (see ICH E10). To use a noninferiority design, the effect size of the comparator that will be present in the new study must be identified to define the noninferiority margin.[5] Currently, there are no known medical products with an effect size adequately characterized to design an adequate noninferiority trial for a new medical product in any SLE setting. A particular problem would also be the inherent variability in outcome and response in different populations. Sponsors considering a noninferiority design should discuss the design with the appropriate review division before trial initiation.

c. Extension trials

If prior evidence suggests clinical activity of the medical product and an acceptable safety profile, sponsors are encouraged to offer patients enrollment into a long-term extension trial to characterize long-term safety. Long-term controlled trial data are preferred over open-label extension safety data because of the difficulty in interpreting adverse event rates in the absence of a concurrent control. Demonstration of long-term benefit would be a critical determination in some settings (e.g., bone marrow transplant).

d. Alternative trial designs

Alternative trial designs, all of which should be designed as superiority trials, include randomized withdrawal, dose-response, and replacement trials. In a replacement trial, patients on a stable standard-of-care regimen should be randomized in a blinded manner to continue that regimen or switch to study treatment. A successful trial would demonstrate better outcomes in the group switched to study treatment. Sponsors should discuss these alternative designs with the review division before initiating these studies.

[5] See 21 CFR 314.126.

3. Study Duration

Clinical trials should be of sufficient length to assess the durability of therapy benefits, taking into account the chronic nature of SLE and its waxing and waning course. In general, a trial evaluating the following endpoints should be at least 1 year in duration: reduction in disease activity, complete clinical response or remission, reduction in flare/increase in time to flare, and maintenance of response. The duration should be based on the onset of action of the medical product and incorporate maintenance therapy for a total of at least 1 year to assess for durability of response as well as safety, depending upon the risks of the medical product.

If the investigational medical product is intended for short-term use, such as induction of response, the total duration of follow-up should still be 1 year, but the investigational medical product does not need to be continued beyond the initial treatment period. In this case, patients can be switched to another maintenance therapy for the remainder of the follow-up period.

Studies investigating treatment of serious acute manifestations of SLE (e.g., acute confusional state, acute transverse myelitis, or acute lupus pneumonitis) are considered a special case of induction therapy. Such studies can also be of relatively short duration depending on the nature of the manifestation, the organ system involved, and the expected time for resolution of the serious acute manifestations under investigation. As for any other trial of induction therapy, a subsequent assessment of the durability of response and safety should be based on data of at least 1-year duration.

4. Study Population

Trials should enroll patients with established SLE, as defined by the American College of Rheumatology classification criteria.

The patient population should reflect the patients who would reasonably be considered for the therapy should it be shown to be effective. It is important that the studied population be one that can be generalized to an appropriate population for recommended use, and not made artificially narrow. However, if existing data (e.g., from exploratory studies) suggest that only a specific, limited population can be expected to benefit from the therapy, the inclusion and exclusion criteria can limit enrollment to that subset of patients with a particular range of disease activity or with a particular serious acute manifestation of SLE. However, as discussed in section III.B.1., Indication, the medical product, if approved, would be labeled to indicate this restricted population.

5. Concomitant Medications

It is important to recognize that changes in concomitant medications, whether steroids, immunosuppressive agents, or other therapies (e.g., angiotensin converting enzyme inhibitors, antihypertensive agents, and agents to control diabetes), can influence outcomes and confound the effect of treatment. Treating physicians should respond to patient needs appropriately, but an attempt should be made in the protocol to define the baseline therapy that is acceptable and

provide guidance on how therapy should be adjusted. Sponsors should collect complete information on use of concomitant medications during trials.

It is important that investigators consider restricting baseline glucocorticoid use (e.g., stable dose or limit the range of doses) to reduce the variability of dosing that may make interpretation of results more difficult. The protocol should specify if glucocorticoid dose changes are allowed during the trial or if patients should be discontinued if they require an increased glucocorticoid dosage.

Potential eligible patients should not be deliberately tapered off their concomitant medications to induce a flare in disease activity for purposes of meeting enrollment criteria in a trial.

We also recommend defining the use of rescue medications and specifying how patients needing such treatment will be treated and analyzed.

6. Stratification

If the effects of treatment are expected to differ substantially in patients with severely active disease as compared to moderately or mildly active disease, it may be desirable to stratify at randomization.

The Systemic Lupus Erythematosus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index was developed, and found to be well-defined and reliable, for measuring organ damage. It may be particularly useful as a means of stratifying patients at trial entry because increased damage has been shown to correlate with a worse prognostic outcome.[6]

If it is expected that particular demographic groups may respond differently to therapy, sponsors also can consider stratification based on a demographic variable.

7. Pediatric Populations

To help standardize the conduct and reporting of pediatric SLE clinical trials and enhance identification of new medical products, the Pediatric Rheumatology International Trials Organization, in collaboration with the Pediatric Rheumatology Collaborative Study Group and with the support of the European Union and the National Institutes of Health, has developed a core set of five domains for the evaluation of response to therapy. These domains include the following:

1. A disease activity index (DAI) (e.g., European Consensus Lupus Activity Measure (ECLAM), Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), Systemic Lupus Erythematosus Activity Measure (SLAM), British Isles Lupus Assessment Group (BILAG), or other DAI deemed appropriate for clinical trials)

[6] Stoll, T, B Seifert, and DA Isenberg, 1996, SLICC/ACR Damage Index Is Valid, and Renal and Pulmonary Organ Scores Are Predictors of Severe Outcome in Patients with SLE, Br. J. Rheumatol, 35:248-54.

2. Renal function (24-hour proteinuria)

3. Parent's global

4. Physician's global

5. Health status (Child Health Questionnaire physical summary score)

Evaluation of response in these five domains can be considered for exploratory use in pediatric SLE trials. Future research will help to establish the degree of change in these domains that represents a clinically important benefit to establish efficacy in clinical trials. Sponsors should discuss the design of pediatric SLE trials with the review division before beginning such trials.

8. Primary Efficacy Endpoints

Sponsors should consider designing clinical trials for medical products to address one or more of the following primary endpoints, as discussed in detail below.

a. Reduction in disease activity

The primary endpoint for a trial evaluating reduction in signs and symptoms of SLE disease activity can be determined using a DAI that has documented evidence of validity, reliability, and ability to detect change in the targeted clinical trial setting. Disease activity scores allow inclusion of patients whose disease affects different organ systems by providing an overall severity score.

Disease activity should be measured at the beginning and end of the trial as well as over the course of the trial. To meet the primary endpoint of the trial, the change in DAI between the outset and the end of the trial should show a statistically significant difference between the treatment groups. It is also important to determine that an improvement in DAI score is not accompanied by a worsening of other disease manifestations. (See also section III.B.14., Risk-Benefit Considerations.)

Several indices exist that mirror the assessment of experienced clinicians and are sensitive to changes in disease activity. The BILAG is the preferred index to study reduction in disease activity in clinical trials. The BILAG scores patients based on the need for therapy; therefore, the clinical interpretation of a change in score is apparent.

Other DAIs include the SLEDAI and Safety of Estrogen in Lupus Erythematosus National Assessment Trial (SELENA)-SLEDAI, the SLAM, and the ECLAM. Updated versions of the BILAG, SLAM, and SLEDAI have been released (BILAG2004, SELENA-SLEDAI/SLEDAI 2K, and SLAM-R). These indices have been shown to be valid in some treatment settings based on the concordance of scores with expert opinion, acceptable interobserver variability among trained evaluators, correlation between individual patient scores on different indices, and correlation between increases in scores and clinical decisions to increase therapy. They also have been shown in cohort studies to be sensitive to changes in disease activity, and can be used

in clinical trials if the instrument measurement properties are adequate for the specific clinical trial setting.[7]

It is important to ensure that the selected DAIs accurately assess disease activity over time. Some DAIs allot points for a new disease manifestation and no points for a stable manifestation. Thus, a disease manifestation that is present at screening and that is stable during the trial can contribute points to the baseline score but no points to subsequent scores leading to an artifactual reduction in the overall disease activity score. The DAIs should also address disease manifestations not caused by SLE and how they will be scored (e.g., hematuria and/or pyuria caused by a urinary tract infection versus lupus nephritis).

If using the BILAG in a 1-year SLE trial, sponsors should conduct an assessment of disease activity at both 6 months and 12 months, as well as at other time points (e.g., monthly) to assess the time course of response. The timing of the primary efficacy analysis, at either 6 or 12 months, depends upon the time it takes for the new medical product to achieve optimal activity. If 12 months is chosen as the primary endpoint, BILAG should show a statistically significant improvement at 12 months that has been sustained at a minimum for 2 months. Alternatively, if the primary endpoint is set at 6 months, clinical benefit should be assessed at 12 months as a secondary endpoint.

In patients with active disease at baseline (defined as one or more BILAG A or two or more BILAG B scores), the primary efficacy analysis using a clinically meaningful benefit can be based on the outcome of major clinical response (MCR) or partial clinical response (PCR), showing a greater frequency in drug-treated patients than in control-treated patients.

An example of the definition of MCR or PCR is presented here. In the example of PCR, flare is defined as the presence of one or more new BILAG A scores or two or more new BILAG B scores. BILAG C scores do not affect the definition of flare, since, by definition, they are not judged to be serious enough to require treatment.

An adjudication committee should be employed to determine which patients meet the predefined outcome. The following factors can be used to define MCR and PCR:

Major Clinical Response

A patient with BILAG C scores or better at 6 months with no new BILAG A or BILAG B scores **AND** maintenance of response with no new BILAG A or B scores between 6 and 12 months.

Partial Clinical Response

A patient with BILAG C scores or better at 6 months with no new BILAG A or BILAG B scores and maintenance of response without a flare for 4 months.

[7] Strand, V, D Gladman, D Isenberg, M Petri, J Smolen, and P Tugwell, 1999, Outcome Measures to Be Used in Clinical Trials in Systemic Lupus Erythematosus, J Rheumatol, 26(2):490-7.

OR

A patient with a maximum of 1 BILAG B score or better at 6 months **AND** maintenance of response without a flare out to 1 year.

OR

A patient with very high disease activity (as defined below) who achieves a maximum of 2 BILAG B scores at 6 months **AND** maintenance of this response without developing a flare out to 1 year. *Very high disease activity* is defined as the presence of one of the following conditions:

- ≥ 2 BILAG A scores (regardless of the number of BILAG B scores)
  OR
- 1 BILAG A score and ≥ 2 BILAG B scores
  OR
- ≥ 4 BILAG B scores (with no BILAG A scores)

A trial of a new medical product's ability to induce response in patients with active disease can also be conducted using a DAI, such as BILAG. In this case, the primary endpoint would be an increase in the proportion of patients with a category C score or better at the end of induction (e.g., 3 or 6 months). Response should be confirmed by repeat measurement at least 1 month later. It is also important that a new medical product not only demonstrate early activity, but also not worsen long-term outcome. Therefore, the maintenance of response also should be assessed as a secondary endpoint at 1 year.

Some treatments may target a biologic mechanism that leads to only certain disease manifestations, or to only disease manifestations related to a single organ system. In these situations, it would usually be preferable to use an organ-specific measure of disease activity as the primary endpoint as opposed to an overall disease activity measure.

The interpretation of a clinical trial using the organ-specific approach can be problematic, however, if improvement in the organ system selected is counterbalanced by worsening manifestations of disease occurring in other organ systems. In addition, results from organ-specific trials may be confounded if changes in treatment regimens are made, such as an increase in immunosuppressive agents (see section III.B.5., Concomitant Medications). Therefore, organ-specific trials should also assess overall disease activity as a secondary endpoint, because the safety information should be taken into consideration in determining the overall risk-benefit assessment of the medical product.

b. Complete clinical response or remission

The primary endpoint for a trial evaluating complete clinical response or remission is defined by the complete absence of disease activity, using a DAI (as described above). The term *response* is used if the patients continue to receive SLE-directed therapies, whereas *remission* is used if patients do not continue to receive ongoing therapy for SLE.

The evaluation of efficacy should be based on the proportion of patients who achieve a BILAG level D score, or zero if using the SLEDAI, in all organ systems for at least 6 consecutive months.

c. Reduction in flare/increase in time to flare

The primary endpoint for a trial evaluating flares can be a reduction in flares or an increase in the time to flare for the new medical product compared to the control group. If time to flare is evaluated as the primary endpoint, the trial should be at least 1 year in duration to evaluate whether the flares are suppressed or only delayed in occurrence. A critical secondary endpoint should be comparison of flare rates or proportion of patients flare-free at an appropriate time point.

A trial assessing flares should randomize patients with quiescent disease (e.g., BILAG C score or better in all organ systems) and assess flares in the group receiving the new medical product compared to the control group.

The definition of flare should be specified in the protocol and should reflect an episode of increased disease activity that correlates with the need for an increase in or change in treatment on clinical grounds. All possible flares should be adjudicated by a data monitoring board that is blinded to treatment.

An index used to measure flare should measure disease activity over a month's period, rather than at fixed time points, in order not to miss any intercurrent flares and to allow full characterization of activity of the medical product over the course of the trial. Acceptable flare indices for clinical trials include the BILAG and SELENA-SLEDAI flare indexes. For example, the BILAG identifies flares as A for severe flare and B for mild to moderate flare. A worsening from an E, D, or C to two or more B scores or one or more A score in any body or organ system during the 1-year trial period can be used to define the occurrence of flare. Time to flare should be the number of days since randomization to occurrence of flare based on BILAG A or B scores.

A trial evaluating maintenance of response can also be considered for a new medical product once active disease (i.e., flares) is in remission (defined as BILAG C or better). Such trials can be a continuation of an induction trial of the new medical product. Patients with active disease who achieve quiescence following induction with a new medical product can be further randomized to switch to placebo or continue the new medical product for the duration of the trial. Alternatively, the induction regimen can consist of a standard-of-care regimen whereby patients are randomized to continue standard of care or are switched to the new medical product for maintenance. The primary endpoint for a trial evaluating maintenance of response can be met by demonstrating an increase (compared to standard of care) in the proportion of patients maintaining a BILAG C score or better at 1 year. If the endpoint is assessed at 6 months, then clinical benefit should also be assessed at 1 year as a secondary endpoint.

d. Reduction in concomitant steroids

Reducing corticosteroid use is an important goal in treatment of patients with SLE if it occurs in the context of a treatment that effectively controls disease activity. Therefore, for a medical product to be labeled as reducing corticosteroid usage, it should also demonstrate another clinical benefit, such as reduction in disease activity as the primary endpoint.

In an add-on trial to test the steroid-sparing potential of a new medical product, patients should be enrolled during a flare and randomized to the addition of the new medical product or placebo to induction doses of corticosteroids. In both study arms, when patients achieve quiescent disease, the corticosteroid dose should be tapered to a maintenance dose that is not usually associated with major toxicities while still maintaining quiescence. The induction steroid dosage and duration of induction therapy and taper schedule should be based on the severity of disease activity in the dominant organ system involved.[8]

The evaluation of efficacy should be based on the proportion of patients in treatment and control groups that achieve a reduction in steroid dose to less than or equal to 10 mg per day of prednisone or equivalent, with quiescent disease and no flares (see definition above) for at least 3 consecutive months during a 1-year clinical trial. For a result to be clinically meaningful, the patient population should be on moderate to high doses of steroids at baseline. Trials should also assess the occurrence of clinically significant steroid toxicities.

e. Treatment of serious acute manifestations

Treatment of serious acute manifestations of SLE can be considered a special case of induction therapy for treatment of SLE emergencies (e.g., acute confusional state, acute transverse myelitis, or acute lupus pneumonitis). The primary endpoints for a trial evaluating treatment of serious acute manifestations should reflect the proportion of patients with improvement after administration of a new medical product or placebo. The improvement should be measured as a lower score in the organ system score on a DAI of the involved organ(s), such that there is no longer a threat to that organ.

As stated in section III.B.3., Study Duration, studies investigating treatment of serious acute manifestations of SLE are considered a special case of induction therapy. Therefore, therapy with the investigational medical product can be of relatively short duration depending on the nature of the manifestation. It is understood that in many cases maintenance therapy will involve a different regimen than the study drug used for induction. Assessment of the durability of response and safety should be obtained after the patient is switched to maintenance therapy for a total of at least 1-year duration.

Trials investigating treatments for serious acute manifestations of SLE can include the following secondary endpoints: time to resolution of the acute manifestation, mortality, need for re-treatment, use of corticosteroids, and overall disease activity as measured by a DAI, such as the SLEDAI or BILAG.

[8] Ad Hoc Working Group on Steroid-Sparing Criteria in Lupus, 2004, Criteria for Steroid-Sparing Ability of Interventions in Systemic Lupus Erythematosus: Report of a Consensus Meeting, Arthritis & Rheum, 50:3427.

Study designs investigating therapies for serious acute manifestations of SLE should be discussed with the review division before beginning trials.

9. Patient-Reported Outcomes

We recognize that improvements in clinical outcome measures (e.g., lab tests, clinical evaluation) in patients with SLE may not always translate to improvements in how patients feel or function. Therefore, we encourage the use of patient-reported outcome (PRO) instruments to measure all relevant and important SLE symptoms and patient-perceived abilities to function and perform daily activities. PRO instrument development should be based upon qualitative research conducted in the target patient population to ensure the content validity of the measure.

Most experts agree that fatigue is an important symptom in SLE. However, experts and patients define fatigue differently. Measurement of fatigue in SLE should include the following: (1) a clear definition of fatigue as it relates to patients with SLE; (2) a clear conceptual framework describing fatigue in SLE including physical and mental components, as appropriate; and (3) methods for measuring fatigue symptoms and effect in the presence of comorbid factors (e.g., depression and medication effects). We have not identified an existing PRO instrument optimal for measurement of fatigue symptom complex in patients with SLE to support labeling claims. Therefore, an exploratory endpoint measure consisting of the use of an existing fatigue measure as well as an open-ended item that asks patients to identify their symptoms could be useful in the development of future instruments for measuring fatigue in SLE.

PRO instruments should be used as key secondary endpoints in all SLE trials. PRO instruments that are intended as key trial endpoints should be demonstrated to be well-defined and reliable in the SLE trial population. We encourage development of new PRO instruments where appropriate. Additional information on how the FDA reviews PRO instruments used to support medical product labeling can be found in the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.

10. Other Endpoints

Endpoints other than those discussed above for consideration in particular SLE trials are discussed here.

a. Damage

An assessment of damage caused by manifestations of SLE disease should be considered for inclusion in SLE trials of at least 1-year duration.

Use of the SLICC/ACR Damage Index measures irreversible organ system damage caused by SLE disease that has been present for at least 6 months. The SLICC/ACR Damage Index assesses damage that accrues over time in the renal, pulmonary, cardiovascular, and other organ systems. It can be used in clinical trials to measure the rate of progression of damage caused by

the disease, or its treatment, but is not sensitive to change unless the time interval for observation is at least 1 year in duration.

An assessment of damage during a trial also can be complicated if a new therapy is associated with toxicities not measured by the Damage Index (e.g., in organs not associated with SLE disease). Therefore, we recommend discussing use of the SLICC/ACR Damage Index or other instrument to assess damage with the review division before beginning trials.

b. Biomarkers

A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. In some cases, biomarkers can assist in the development and evaluation of therapies for SLE by supporting a hypothesized mechanism of action or by suggesting an appropriate dose or duration of action.

Surrogate endpoints are a subset of biomarkers that are expected to predict clinical benefit (or harm or lack of benefit) and are intended to substitute for a clinical endpoint.[9] Currently, none of the known biomarkers (e.g., anti-dsDNA levels, complement levels) in SLE has been validated as a surrogate endpoint, and therefore no biomarker can substitute for a direct assessment of clinical benefit in clinical trials.

In some cases, biomarkers are used to define risk or identify potential responders to a treatment. Sponsors should consult the appropriate FDA center to determine whether a biomarker used to select patients or monitor response in clinical trials can be used in prescribing the medical product if it is approved (e.g., for selection of patients or for monitoring safety or effectiveness).[10]

11. Study Procedures and Timing of Assessments

In SLE trials using reduction in disease activity as an endpoint, it is important that the protocol specify procedures to ensure that the scoring of the DAI specifically reflects SLE-related organ dysfunction. The interpretation of score changes can be confounded if organ system dysfunction caused by a disease or condition other than SLE is present or organ dysfunction caused by the treatment occurs. Investigators should be appropriately trained to ensure uniform scoring, as variability can decrease study power. In some cases, it may be helpful to have an adjudication committee confirm assessment based on DAIs (e.g., flares or quiescence of disease).

12. Statistical Considerations

The particular statistical analysis used can differ depending on the endpoints and outcomes of interest. To assess a reduction in disease activity or flare, induction of response, treatment of

[9] Biomarkers Definitions Working Group, 2001, Biomarkers and Surrogate Endpoints: Preferred Definitions and Conceptual Framework, Clin Pharm Therap, 69(3):89-95.

[10] Contact CBER or CDRH's Office of In Vitro Diagnostic Devices Evaluation and Safety.

serious acute manifestations, or maintenance of response, the statistical test usually should evaluate the difference between the treatment and control groups in the proportion of patients meeting a predefined outcome, although measures of continuous variety also can be useful. These outcomes can be summarized as binary or ordinal for the purpose of the primary analysis. Although outcomes at the end of the trial are usually the primary focus, outcomes also should be evaluated at multiple times during the trial. To assess the time to flare in patients with quiescent disease, the statistical test usually would evaluate the difference in the time-to-event curves using an appropriate test. This analysis also should be supported by an analysis comparing the proportion of flare-free patients at the end of the trial. Analysis considerations of primary endpoints for organ-specific disease should be similar to those for SLE.

In addition to the primary assessments of disease activity, other aspects of the disease process may be important in fully elucidating the effect of the treatment on patients. The overall probability of a false positive finding for a completely ineffective treatment should be controlled by prespecifying a single primary analysis or several analyses with appropriate adjustment for multiplicity. Secondary analyses also should be adjusted to avoid error and the protocol should describe the plan for controlling such errors.

We recommend prespecifying in the protocol statistical approaches (e.g., regarding dropouts or missing data) (see ICH E9).

13. Accelerated Approval Considerations for Human Drugs and Therapeutic Biological Products (Subpart H and Subpart E)

For serious or life-threatening conditions, a new human drug (21 CFR part 314, subpart H) or therapeutic biological product (21 CFR part 601, subpart E) can be approved on the basis of adequate and well-controlled clinical trials that establish that the human drug or therapeutic biological product has an effect on a "surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit" (21 CFR 314.510 and 21 CFR 601.40). Full approval would be contingent on required postmarketing clinical trials to verify the clinical benefit.

No surrogate marker has been reliably shown to predict clinical benefit in patients with SLE and there has been no Subpart H or Subpart E approval of medical products for SLE. Sponsors should be very cautious about selecting a potential surrogate marker intended to support accelerated approval until there is confidence regarding its predictive value.

14. Risk-Benefit Considerations

Assessment of risks and benefits involves an appraisal of the effect of the medical product on all aspects of the disease process, including disease activity, irreversible damage caused by the disease or its treatment, and health-related quality of life.[11] The primary efficacy analysis should show a statistically significant result and the measured clinical effect of the medical product should be clinically meaningful. Toxicities related to the pharmacologic effects of the medical

[11] Strand, V, D Gladman, D Isenberg, et al., 1999, Outcome Measures to Be Used in Clinical Trials in Systemic Lupus Erythematosus, J Rheumatol, 26:490-7.

product (e.g., immunosuppression) also should be considered as part of this overall risk-benefit assessment of the medical product.

It is important that the size of the safety database for human drugs and therapeutic biological products at approval be consistent with the recommendations made in the ICH guidance for industry *E1A The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions*. Particular attention should be paid to the assessment of known toxicities, or to pharmacologic and biological effects that might be suspected to imply delayed toxicities. It is important to consider these toxicities in formulating the clinical development program. This information may influence the size of the safety database.

A smaller safety database may be appropriate to support approval of medical products designed to treat aspects of SLE that represent orphan indications or for the treatment of serious acute manifestations, because it may be impossible or impractical to study a large number of patients with these conditions.[12] Sponsors may wish to discuss these issues with the appropriate review division early in the development of a new treatment.

Finally, if there is concern about rare but serious adverse events (e.g., from the mechanism of action or experience with similar human drugs and therapeutic biological products), a postmarketing study or clinical trial may be needed to gather additional safety information.

[12] For information regarding orphan indications, see the following Web site: http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/ucm135122.htm.

Guidance for Industry

Lupus Nephritis Caused By Systemic Lupus Erythematosus — Developing Medical Products for Treatment

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

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Guidance for Industry

Lupus Nephritis Caused By Systemic Lupus Erythematosus — Developing Medical Products for Treatment

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Lupus Nephritis Caused By Systemic Lupus Erythematosus — Developing Medical Products for Treatment

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I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the clinical development of medical products (i.e., human drugs, therapeutic biological products, and medical devices) for the treatment of lupus nephritis (LN) caused by systemic lupus erythematosus (SLE). Specifically, this guidance addresses the Food and Drug Administration's (FDA's) current thinking regarding study population enrollment and efficacy endpoints for LN trials. This guidance is intended to serve as a focus for continued discussions among the FDA, medical industry, sponsors, academic community, and the public.[2] As the science of this indication evolves, this guidance may be revised.

This guidance applies to developing medical products to treat SLE disease with a focus on kidney manifestations, and finalizes the parts of the draft guidance for industry *Systemic Lupus Erythematosus — Developing Drugs for Treatment* (published March 2005) regarding LN. SLE disease affecting organs other than the kidney will be addressed in separate guidances. If sponsors wish to study other organ-specific forms of disease, they are encouraged to contact the appropriate review division.

Sponsors should become familiar with the guidance for industry, *Systemic Lupus Erythematosus — Developing Medical Products for Treatment* (SLE guidance), for information regarding the

[1] This guidance has been prepared by the Systemic Lupus Erythematosus Working Group, which includes representatives from the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), the Center for Devices and Radiological Health (CDRH), and the Office of Critical Path Programs (OCPP) in the Office of the Commissioner (OC) at the Food and Drug Administration.

[2] In addition to consulting guidances, sponsors are encouraged to contact the relevant division to discuss specific issues that arise during the development of medical products for the treatment of LN caused by SLE.

overall development program and clinical trial designs for general SLE disease.[3] The SLE guidance provides general information on clinical trial considerations that may assist sponsors in studying LN, as well as providing specific information on trial design, trial duration, efficacy endpoints, and response criteria in SLE.

This guidance does not contain discussion of the general issues of clinical trial design or statistical analysis. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical Trials*. This guidance focuses on specific medical product development and trial design issues that are unique to the study of LN caused by SLE.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Although LN is the most commonly studied organ-specific manifestation of SLE, there is at present no approved therapy. When long-standing and persistently active, LN causes end-stage renal disease (ESRD) and death. Also, the occurrence of renal flares has been shown to predict progression to doubling of serum creatinine.[4]

Current standard-of-care treatment for LN consists of corticosteroids and immunosuppressives. With such regimens, the prognosis for LN has improved considerably, and the occurrence of renal failure is uncommon.[5] In addition, treatment that induces remission of active LN has been shown to be associated with a reduced risk of progression to ESRD.[6,7] However, not all patients respond adequately. Adverse outcomes in patients with LN can arise both from consequences of the disease and adverse effects of these therapies. Therefore, there is an unmet medical need for more effective and less toxic treatments.

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[3] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Guidances Web page at http://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[4] Ponticelli, C and G Moroni, 1998, Flares in Lupus Nephritis: Incidence, Impact on Renal Survival and Management, Lupus, 7;635-638.

[5] Grootscholten, C, IM Bajema, S Florquin, et al., 2007, Treatment with Cyclophosphamide Delays the Progression of Chronic Lesions More Effectively than does Treatment with Azathioprine plus Methylprednisolone in Patients with Proliferative Lupus Nephritis, Arthritis & Rheum, 56:924-37.

[6] Korbet, SM, EJ Lewis, MM Schwartz, M Reichlin, J Evans, and RD Rohde, 2000, Factors Predictive of Outcome in Severe Lupus Nephritis, American Journal of Kidney Diseases, 35(5);1-12.

[7] Mok, CC, KY Ying, S Tang, Y Leung, KW Lee, WL Ng, RWS Wong, and CS Lau, 2004, Predictors and Outcome of Renal Flares after Successful Cyclophosphamide Treatment for Diffuse Proliferative Lupus Glomerulonephritis, Arthritis & Rheum, 50(8);2559-3568.

III. DEVELOPMENT PROGRAM CONSIDERATIONS SPECIFIC TO LUPUS NEPHRITIS

The following sections provide recommendations specific to the development of medical products for the treatment of LN. These recommendations should be considered along with the recommendations provided in the SLE guidance. Even though this guidance focuses on the evidence of effectiveness of medical products for LN, other end organs are also affected by SLE, and disease manifestations in these other organ systems should also be followed clinically during LN trials.

Demonstration that a medical product prevents progression to ESRD in LN clinical trials obviously would be evidence of effectiveness, but it is not likely that this will be shown, given how infrequently ESRD occurs with current standard-of-care treatment. Because both induction of renal remission and reduction in renal flares have been shown to lead to preservation of renal function, they are valid effectiveness endpoints in LN clinical trials.

A. Study Population

Phase 3 clinical trials designed to assess clinical benefit of a medical product for the treatment of LN should enroll patients with established SLE (as defined by the American College of Rheumatology classification criteria), biopsy-proven proliferative glomerulonephritis (World Health Organization (WHO) grades III or IV; or Class III or IV using the 2003 International Society of Nephrology/Renal Pathology Society (ISN/RPS) criteria), or membranous glomerulonephritis (WHO grade V or ISN/RPS Class V). The distribution of the various histologic types of nephritis in a trial should be representative of the overall population of patients with LN, unless an investigational medical product is expected to affect only a particular histologic type. If that is the case, trials should be designed to enrich for that particular subset of the population. When feasible, baseline biopsies also should be assessed for the percent of sclerosed glomeruli, because this endpoint has been suggested to be predictive of long-term outcome.[8] (See section III.F., Other Endpoints.)

To be eligible for enrollment, a patient should have documentation of a biopsy within the preceding 12 months. In addition, the patient should have documentation of active renal disease at screening, as evidenced by active urinary sediment and proteinuria. An assessment of renal function is not included in the definition of active renal disease for the purposes of enrollment, because patients may present with active LN yet have initially normal renal function. However, renal function should be measured at baseline and during clinical trials to assess any changes in renal function while on therapy. An assessment of renal function should be included in the composite definition of renal response (see section III.D.1., Induction and Maintenance of Renal Remission).

[8] Grootscholten, C, IM Bajema, et al., 2007, Treatment with Cyclophosphamide Delays the Progression of Chronic Lesions More Effectively than does Treatment with Azathioprine plus Methylprednisolone in Patients with Proliferative Lupus Nephritis, Arthritis & Rheum, 56:924-937.

The following factors used to define active renal disease can be used for enrollment purposes:

1. Urinary protein:creatinine ratio ≥ 0.5

   AND

   Active urinary sediment as defined by ≥ 1 of the following (in the absence of urinary tract infection):
   - > 5 red blood cell (RBC)/high power field (hpf) (or above the reference range for the laboratory)
   - > 5 white blood cell (WBC)/hpf (or above the reference range for the laboratory)
   - Presence of cellular casts (RBC or WBC)

2. Patients with proteinuria alone and without active sediment also can be enrolled if they have a level of proteinuria at baseline that warrants treatment (e.g., ≥ 3.5 grams/day).

Consideration should be given to stratifying LN patients based upon whether or not they received treatment or on the type of treatment received between undergoing a renal biopsy within the past 12 months and the time of enrollment in a trial. Stratification also can be based on presence or degree of baseline renal impairment, although the renal function may not be always correlated with the severity of the diseases. The final clinical outcome of the renal impairment will depend on the histopathology findings such as the acute inflammation or the chronic glomerulosclerosis.

B. Study Duration

Clinical trials should be of sufficient length to assess the durability of therapy benefits, taking into account the chronic nature of LN and its waxing and waning course. In general, a trial should be at least 1 year in duration to assess for durability of response as well as safety, depending upon the risks of the medical product.

If the investigational medical product is intended for short-term use, such as induction of renal remission, the total duration of follow-up should still be at least 1 year, but the investigational medical product does not need to be continued beyond the initial treatment period. In this case, patients can be switched to another maintenance therapy for the remainder of the follow-up period.

C. Study Design

The preferred design for efficacy trials is a parallel arm, randomized, controlled superiority trial using placebo or active control. At this time, a noninferiority design is not possible because there are no known medical products with an effect size adequately characterized to design a trial. For a description of other possible designs, see the SLE guidance.

One example of an add-on design that assesses superiority of a new medical product would be a trial of corticosteroids and cyclophosphamide plus placebo compared to corticosteroids and cyclophosphamide plus new medical product. However, demonstration of an efficacy benefit of a new medical product may be difficult in trials in which cyclophosphamide, azathioprine, or mycophenolate mofetil are considered part of the standard-of-care regimen because of the activity of these agents or if the mechanism of action of the standard-of-care drugs and the new medical product are similar.

In principle, a randomized, withdrawal trial also can be considered. In this design, after patients achieve a response, they are randomized either to be withdrawn from the new medical product and continue to receive the active control alone or to continue to receive the new medical product plus active control. The efficacy endpoint would be demonstration of superiority of the treatment arm that received continued use of the new medical product compared to the withdrawal arm.

D. Primary Efficacy Endpoints

Sponsors should consider designing clinical trials for medical products to address the following primary endpoints: *induction of renal remission*, *maintenance of renal remission*, and *reduction in renal flares/increase in time to renal flare*.

1. Induction and Maintenance of Renal Remission

The primary composite endpoint in a trial of renal remission should include changes in urinary sediment (i.e., hematuria, pyuria, and cellular casts), proteinuria, and renal function. As noted in section III.A., Study Population, although impairment of renal function is not needed to meet the definition of active renal disease for enrollment purposes, an assessment of renal function is included in the definition of renal response. To demonstrate a complete renal response, all baseline abnormalities in any of these three components should normalize.

Studies have shown that achieving renal remission is associated with a reduced risk of developing renal insufficiency (see section II., Background). However, to assess the safety of new medical products for LN, sponsors should also include an evaluation of the occurrence of ESRD and doubling of serum creatinine in a multiyear trial. Such a trial can be conducted as a postmarketing requirement (see section III.E., Secondary Efficacy Endpoints).

The following is a discussion of the individual components included in the primary composite endpoint of renal remission. A clinical trial should include all three components in the composite endpoint because the individual components are not adequate to assess clinical outcome. However, the components should also be evaluated individually as secondary endpoints (see section III.E., Secondary Efficacy Endpoints).

1. *Urinary sediment*. An assessment of urinary sediment for quantitative changes in cellular casts, hematuria, and pyuria, when measured accurately, is considered a sensitive indicator of the level of LN activity. Local or central laboratories can be used as long as

the analysis method is shown to be accurate and reproducible. It is desirable to outline standardized methods for collecting and analyzing urine samples in the protocol.

2. *Proteinuria*. Changes in the urine protein/creatinine ratio can serve as an assessment of the extent of proteinuria. Estimates of protein excretion based on timed urine collection also can be used, but it is critical for sponsors to document the completeness of the collection (e.g., based on creatinine excretion) because timed collections have been shown to be frequently incomplete.[9]

3. *Renal function*. In those patients with a decreased creatinine clearance at baseline, failure to normalize renal function in response to therapy may indicate an increased risk of progression to renal failure.[10] Renal function can be assessed based on measured creatinine clearance (24-hour creatinine clearance), estimated creatinine clearance (Cockcroft-Gault formula), estimated glomerular filtration rate (Modification of Diet in Renal Disease (MDRD), MDRD formula), or measured iothalamate clearance, among others.[11,12] Investigators should design trials to minimize confounding variables (e.g., overdiuresis and use of concomitant medications, such as nonsteroidal anti-inflammatory agents and angiotensin-converting enzyme inhibitors) because they can complicate interpretation of renal function measures, including serum creatinine and creatinine clearance.[13]

Patient response using the composite endpoint should be defined as complete, partial, or no response. To demonstrate a complete renal response, all baseline abnormalities in sediment, protein, and renal function should return to normal. A response should be confirmed by repeat measurement at least 1 month later. The evaluation of efficacy should be based on the comparison of the proportion of patients who achieve complete, partial, or no response across the treatment groups. Statistical analysis of the ranked outcomes of complete, partial, and no response should be performed using an appropriate statistical test.

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[9] Renal Disease Subcommittee of the American College of Rheumatology Ad Hoc Committee on Systemic Lupus Erythematosus Response Criteria, 2006, The American College of Rheumatology Response Criteria for Proliferative and Membranous Renal Disease in Systemic Lupus Erythematosus Clinical Trials, Arthritis & Rheum, 54(2):421-432.

[10] Levey, AS, SP Lan, HL Corwin, BS Kasinath, et al., 1992, Progression and Remission of Renal Disease in the Lupus Nephritis Collaborative Study: Results of Treatment with Prednisone and Short-Term Oral Cyclophosphamide, Ann Int Med, 116:114-123.

[11] Cockcroft, DW and MH Gault, 1976, Prediction of Creatinine Clearance from Serum Creatinine, Nephron, 16:31-41.

[12] Levey, AS, JP Bosch, JB Lewis, et al., 1999, A More Accurate Method to Estimate Glomerular Filtration Rate from Serum Creatinine: A New Prediction Equation, Modification of Diet in Renal Disease Study Group, Ann Int Med, 130:461-70.

[13] Boumpas, DT and JE Balow, 1998, Outcome Criteria for Lupus Nephritis Trials: A Critical Overview, Lupus, 7:622-629.

For example, a complete renal response or a partial renal response can be defined as follows:

Complete Renal Response

Calculated glomerular filtration rate (GFR) is within the normal range

AND

Inactive urinary sediment (< 5 RBCs/hpf and < 5 WBCs/hpf (or within the reference range of the laboratory); and no cellular casts (no RBC or WBC casts)

AND

Urinary protein:creatinine ratio < 0.5

For patients with a normal urinary sediment and GFR at baseline and only the presence of proteinuria (≥ 3.5 grams/day), the urine protein:creatinine ratio should be less than 0.5 to meet the primary endpoint.

Partial Renal Response

Estimated GFR no more than 10% below the baseline value

AND

RBCs/hpf ≥ 50% reduction from baseline and no RBC casts

AND

≥ 50% improvement in the urine protein:creatinine ratio with one of the following:

– a urine protein:creatinine ratio of < 1.0, if the baseline ratio was ≤ 3.0

OR

– a urine protein:creatinine ratio of < 3.0, if the baseline ratio was > 3.0

2. Reduction in Renal Flares/Increase in Time to Renal Flare

An increase in the frequency and severity of flares in LN correlates with a poor outcome.[14] An established definition of flare can be used as the primary endpoint in a trial designed to demonstrate a decreased frequency, or decreased severity, of flares.

[14] Moroni, G, S Quaglini, M Maccario, et al., 1996, Nephritic Flares Are Predictors of Bad Long-Term Renal Outcome in Lupus Nephritis, Kidney International, 50:2047-53.

A success in a clinical trial can be defined as a decrease in the number of flares or as an increase in the time to flare for the new medical product compared to the control group over the course of a 1-year trial. If time to flare is evaluated as the primary endpoint, a critical secondary endpoint should be comparison of flare rates or proportion of patients flare-free at an appropriate time point.

The following definition of *renal flare* consisting of the development of one or more of the following three factors is recommended for use in clinical trials.[15]

Increased Proteinuria

A urinary protein:creatinine ratio > 0.5, provided the 24-hour urine protein contains a total of at least 500 mg of protein.

OR

A reproducible increase in 24-hour urine protein levels to:

> 1,000 mg if the baseline value was < 200 mg

OR

> 2,000 mg if the baseline value was between 200 and 1,000 mg

OR

More than twice the value at baseline if the baseline value was > 1,000 mg

Impaired Renal Function

A reproducible decrease in GFR of > 20%, accompanied by proteinuria (> 1,000 mg/24 hours), hematuria (≥ 4 RBCs/hpf or above the reference range for the laboratory), and/or cellular (RBC and WBC) casts

New Hematuria

New, reproducible hematuria (≥ 11 to 20 RBCs/hpf) or a reproducible increase in hematuria by 2 grades compared with baseline, associated with > 25% dysmorphic RBCs, glomerular in origin, exclusive of menses, accompanied by either an 800 mg increase in 24-hour urinary protein levels or new RBC casts.

If sponsors wish to use an alternative definition of renal flare, then they should provide data to support their definition to the review division in advance of conducting such trials.

[15] Alarcon-Segovia, D, JA Tumlin, RA Furie, et al., 2003, LJP 394 for the Prevention of Renal Flare in Patients with Systemic Lupus Erythematosus, Arthritis & Rheum, 48:442-54.

E. Secondary Efficacy Endpoints

Urinary sediment, proteinuria, and renal function are components of the composite primary endpoints for various LN trials, but these parameters should also be evaluated individually in all trials as secondary endpoints. The use of the doubling of serum creatinine has been shown to reliably predict long-term renal outcome. Therefore, preservation of renal function can be assessed using either doubling of serum creatinine or progression to ESRD.

- Doubling of serum creatinine is defined as the proportion of patients whose serum creatinine attains a level double that of the baseline value and is confirmed with a second measurement at least 3 weeks later.

- Progression to ESRD is defined as the need for chronic dialysis or renal transplantation.

Other secondary endpoints that should be included in all LN trials include outcomes using a patient global response, and an assessment of overall disease activity (using the British Isles Lupus Assessment Group or other disease activity index).

For LN trials evaluating induction or maintenance of renal remission as the primary endpoint, the duration of response should be included as a secondary endpoint.

In addition to evaluating renal function during a 1-year clinical trial, sponsors also should assess the potential safety risk of the medical product to cause a delayed deterioration in renal function. The assessment of long-term effects on renal outcome generally can be conducted as a postmarketing requirement in the form of a multiyear follow-up trial using the endpoints previously discussed to assess preservation of renal function.

F. Other Endpoints

In addition to the other endpoints discussed in the SLE guidance (i.e., damage and biomarker endpoints), renal histology can be considered as an endpoint for LN trials to confirm renal response. When feasible, renal biopsies should be obtained at the end of a trial evaluating renal response or remission to demonstrate that an improved renal response corresponds to a histologic improvement, including effects on the percent of sclerosed glomeruli. If it is not possible to obtain biopsies on all patients, biopsies should be obtained from a predefined subset of patients. Sponsors may wish to stratify patient enrollment based upon whether or not a post-treatment biopsy will be obtained.

Guidance for Industry

Suicidality: Prospective Assessment of Occurrence in Clinical Trials

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Thomas Laughren at 301-796-2260.

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Suicidality: Prospective Assessment of Occurrence in Clinical Trials

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I. INTRODUCTION

The purpose of this guidance is to assist sponsors in prospectively assessing the occurrence of treatment-emergent suicidality in clinical trials of drug and biological products.[2] Specifically, this guidance addresses the Food and Drug Administration's (FDA's) current thinking regarding the importance of suicidality assessment in psychiatric and nonpsychiatric drug trials and the general principles for how best to accomplish this assessment during drug development.

The principles discussed in this guidance for the prospective assessment of suicidality involve actively querying patients about the occurrence of suicidal thinking and behavior, rather than relying on patients to report such occurrences spontaneously, followed by retrospective classification of events into appropriate categories. This guidance recommends a specific suicidality assessment instrument that can be used to conduct such prospective assessments and offers guidance on the use of alternative instruments.

This guidance intends to serve as a focus for continued discussions among the FDA, pharmaceutical sponsors, the academic community, and the public.[3] This guidance does not address the complex analytic issues involved in the analysis of the suicidality data that will be derived from prospective assessments of suicidality; these issues will be addressed in separate guidances.

[1] This guidance has been prepared by the Division of Psychiatry Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

[3] In addition to consulting guidances, sponsors are encouraged to contact the relevant review division to discuss specific issues that arise during the development of specific drugs.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Suicidality is a broad term that includes both suicidal ideation and behavior, both nonfatal and fatal suicide attempts, that occur during drug treatment. There has been much focus on treatment-emergent suicidality in recent years, and the question of how best to assess this type of event in future trials has been raised. The concern has resulted in part from findings of apparent treatment-emergent suicidality caused by several different types of drugs. Meta-analyses of placebo-controlled antidepressant trials, both pediatric[4] and adult,[5] revealed a signal for drug-related treatment-emergent suicidality at the younger end of the age spectrum. A meta-analysis of placebo-controlled trials of antiepileptic drugs, including drugs with diverse pharmacology in studies of epilepsy as well as psychiatric indications, also revealed a signal for drug-related treatment-emergent suicidality.[6] In all of the trials involved in these meta-analyses, the suicidality events were identified and classified retrospectively; that is, the trials were not designed to prospectively identify such events. Perhaps as a result, relatively few cases were identified in this effort, the case descriptions were not complete, and baseline status was not well-defined.

A concern about treatment-emergent suicidality has arisen for nonpsychiatric drugs as well (in addition to antiepileptic drugs), based mostly on spontaneous reports. These drugs have included isotretinoin and other tretinoins, beta blockers, reserpine, smoking cessation drugs, and drugs for weight loss. Given the wide range of drugs involved, it is reasonable to consider whether prospective assessments for suicidality should be included in clinical trials involving at least selected drugs for nonpsychiatric indications.

There are two reasons for prospectively assessing suicidality in clinical trials. The first is to ensure that patients in clinical trials who are experiencing suicidality are properly recognized and adequately treated. The second is to ensure the collection of more timely (i.e., closer to the event) and more complete data on suicidality than have been collected in the past, so that in the future we will be better able to detect increased suicidality in individual studies and in pooled analyses. This is important whether or not a particular drug is known to be associated with treatment-emergent suicidality. In the following sections, general recommendations are provided

[4] Hammad, TA, T Laughren, and J Racoosin, 2006, Suicidality in Pediatric Patients Treated With Antidepressant Drugs, Arch Gen Psychiatry, 63:332-339.

[5] Stone, M, T Laughren, ML Jones, M Levenson, PC Holland, A Hughes, TA Hammad, R Temple, and G Rochester, 2009, Risk of Suicidality in Clinical Trials of Antidepressants in Adults: Analysis of Proprietary Data Submitted to U.S. Food and Drug Administration, BMJ, 339:b2880.

[6] FDA, 2008, FDA Advisory: Suicidality and Antiepileptic Drugs (http://www.fda.gov/cder/drug/Infopage/antiepileptics/default.htm).

for prospective assessment of suicidality occurrence, applicable to any drug, followed by a discussion of which drugs should be assessed for suicidality in addition to drugs for psychiatric indications.

III. PROSPECTIVE ASSESSMENT OF SUICIDALITY OCCURRENCE — GENERAL RECOMMENDATIONS

A. Suicidality Assessment Instruments

We recommend use of a suicidality assessment instrument that maps to the Columbia Classification Algorithm for Suicide Assessment (C-CASA).[7] The C-CASA was developed to assist the FDA in coding suicidality data accumulated during the conduct of clinical trials of antidepressant drugs. It provides a set of preferred terms for use in coding, a critical step in preparation for analysis of these data, and the FDA has adopted the C-CASA as the standard for coding suicidality data. The nine C-CASA codes are as follows (see Appendix A for the definitions of these codes):

1 Completed Suicide
2 Suicide Attempt
3 Preparatory Actions Toward Imminent Suicidal Behavior
4 Suicidal Ideation
5 Self-Injurious Behavior Intent Unknown
6 Fatal Event: Not Enough Information
7 Self-Injurious Behavior Without Suicidal Intent
8 Other (Accident, Psychiatric, Medical)
9 Nonfatal Event: Not Enough Information

These codes were developed to assist the FDA in retrospectively classifying events that were captured on the basis of their being possibly suicide-related. This process was necessary to conduct the previously noted antidepressant meta-analyses. Possibly suicide-related events were captured by searching electronic databases using search strings, and by evaluating all deaths and other serious adverse events for possible suicidality. As prospective assessments for suicidality are adopted, certain of these codes become irrelevant for patients who can be assessed.

- Codes 1 to 4 are the events that the FDA considers to represent *suicidality*, and these are the events that would be likely to be included in any subsequent meta-analyses.

- Code 7 represents a nonsuicidal event, but should nevertheless be captured because it has some predictive value for future suicidality, and might be useful for certain analyses.

- Codes 5, 6, and 9 are indeterminate categories, and are unnecessary for prospectively assessed patients. Any deaths in a clinical trial would of course be explored with

[7] Posner, K, MA Oquendo, M Gould, B Stanley, and M Davies, 2007, Columbia Classification Algorithm of Suicide Assessment (C-CASA): Classification of Suicidal Events in the FDA's Pediatric Suicidal Risk Analysis of Antidepressants, Am J Psychiatry, 164:1035-1043.

sufficient depth to determine, if possible, whether or not they should be classified as suicides, and this information would be captured on the assessment form. If they remain indeterminate, there is no need to code the information. Similarly, any self-injurious behaviors and suspicious accidents would be explored as part of the prospective assessment. Again, if such events remain indeterminate, there is no need to code the information.

- Events that would code to 8 (e.g., events that represent accidents, psychiatric, or other medical events) need not be captured.

One such assessment instrument is the Columbia Suicide Severity Rating Scale (C-SSRS).[8] It involves a series of probing questions to inquire about possible suicidal thinking and behavior, and this process should be conducted at baseline and at each patient visit. The information collected is immediately classified into the C-CASA categories as the interview is conducted (i.e., information pertinent to suicidality is *mapped* to the C-CASA categories as part of the assessment). The C-SSRS is a detailed interview, but it is needed only if the initial screening questions about suicidality are positive. Although the screening questions should be completed at baseline and at every visit for every patient, they are not by themselves burdensome. There are likely to be several different approaches to administering the C-SSRS, including investigator-administered or self-report (e.g., phone, computer). Alternative approaches may be appropriate as long as the method is validated. Sponsors can use other appropriate prospective suicidality assessment instruments, but should discuss alternative instruments with the appropriate review division.

The following information can be used by sponsors to evaluate the appropriateness of other proposed instruments:

- <u>Domains</u>: *The instrument should include all the key concepts (domains) identified in C-CASA:*
  - *Suicidal ideation:*
    - *Passive (wish to be dead)*
    - *Active (4 levels)*
      - *Nonspecific (no method, intent, or plan)*
      - *Method, but no intent or plan*
      - *Method and intent, but no plan*
      - *Method, intent, and plan*
  - *Suicidal behavior*
    - *Actual attempt*
    - *Preparatory actions toward imminent suicidal behavior*
      - *Interrupted*
      - *Aborted*
      - *Preparatory acts or behaviors*
  - *Nonsuicidal self-injurious behavior*

[8] See http://www.cssrs.columbia.edu.

- *Definitions: The instrument should include definitions for all of these concepts (these definitions should coincide with the definitions in C-CASA).*

- *Probes/Questions: The instrument should include probe questions that permit determination of whether or not each of these ideas or behaviors occurred.*

- *Other information: The instrument should provide for integration of information from other sources (e.g., emergency room visit, death certificate) to permit accurate completion of the assessment.*

- *Mapping to C-CASA: It should be possible to directly code from the responses recorded on the instrument to C-CASA categories (especially 1, 2, 3, and 4), without any additional effort (e.g., creation and blinded rating of narratives). Other instruments, in conjunction with other assessments in a particular program, may collect the data necessary for coding to C-CASA terms, but may not accomplish the actual coding. In those instances, narratives should be created and blinded classification of the narratives conducted if the data were to be used in a meta-analysis.*

- *Training: There should be provision for formal training of raters to ensure reasonable accuracy and consistency in application of the instrument.*

- *Psychometrics: The psychometric properties of the instrument should be well-established.*

B. General Advice on Management of Suicidality Data

This section provides general advice regarding management of suicidality data derived from prospective assessments of suicidality in clinical trials. Detailed advice about the structure of data tables and other data recommendations for preparing a suicidality submission to the FDA will be discussed in a separate guidance, as well as analytic and statistical considerations. Although this guidance continues to use the broad term suicidality to refer to events coded as 1 through 4 of C-CASA, and suicidality was the primary endpoint in previous FDA meta-analyses, it is likely that future meta-analyses will focus on suicidal behaviors and ideation separately, because previous analyses have found somewhat different results for these different concepts and they may have different predictive value. Nevertheless, the broad term suicidality continues to have value as an overall category for events of interest in this general domain.

A critical component of any prospective assessment for suicidality is that it be designed for the immediate coding of collected data to C-CASA categories as part of the assessment process. Thus, appropriate instruments will not require the creation of narratives for blind assessment by experts in suicidality before data analysis, as was the case for previous FDA meta-analyses. It should be necessary only to collapse the data from any instrument used for a particular patient for a particular assessment interval into a coding form for that patient for that particular interval that simply acknowledges whether or not the patient experienced the events of interest at least one time during that interval. Because the events are not mutually exclusive, it is possible for a

patient to have more than one type of event during an interval. For example, during a reporting interval, a patient might have experienced separate instances of suicidal ideation, self-injury without suicidal intent, suicide attempt, and completed suicide. In previous meta-analyses, the FDA counted only the most serious suicidality event during an interval, but different approaches might be used in future analyses. Consequently, all discrete events should be separately coded and recorded (i.e., C-CASA codes 1, 2, 3, 4, and 7). As noted, with prospectively assessed patients, codes 5, 6, 8, and 9 are no longer relevant and need not be captured on the coding forms. Appendix B provides a coding form that can be used for coding and summarizing suicidality data for individual patients.

Following is a mapping algorithm that should be applied for the C-SSRS:

1. Completed Suicide: Only a completed suicide would map to this code.

2. Suicide Attempt: Only a nonlethal suicide attempt would map to this code.

3. Preparatory Actions Toward Imminent Suicidal Behavior: Any of the following events would map to this code, assuming they were not part of an event that met criteria for an actual suicide attempt:
   - Interrupted
   - Aborted
   - Preparatory acts or behaviors

4. Suicidal Ideation: Any of the following events would map to this code, assuming they were not part of an event that met criteria for a preparatory action or an actual suicide attempt:
   - Passive (wish to be dead)
   - Active (4 levels)
     - Nonspecific (no method, intent, or plan)
     - Method, but no intent or plan
     - Method and intent, but no plan
     - Method, intent, and plan

7. Self-Injurious Behavior Without Suicidal Intent: Any events meeting the definition for this term would be mapped.

C. Specific Trial Considerations

1. Determining Trials for Suicidality Assessment

In general, suicidality should be assessed in every trial once it has been determined that the drug is appropriate for this assessment. The full assessment of suicidality generally should involve a pooled analysis of all controlled trials, so it will not be possible to conclude that the suicidality question has been resolved until all data are in hand.

2. Challenging Populations in Which to Assess Suicidality

It is reasonable to omit, or consider alternative assessments, in trials involving patients with cognitive impairment that is so substantial as to interfere with an understanding of the concept of suicide. Such populations include patients with Alzheimer's disease, other dementias, mental retardation, and autism.

A sponsor considering the omission of standard suicidality assessments (where these generally would be conducted) from a particular clinical trial in a particularly challenging population should discuss this omission with the FDA to gain prior agreement. In certain instances, alternative instruments may permit the assessment of suicidality or other adverse psychological events. Instruments such as the C-SSRS have been used successfully in children and adolescent patients with various psychiatric disorders that do not involve cognitive impairment.

3. Dosing Considerations

a. Single-dose trials

The time course of the risk for drug-induced suicidality is unknown and may be different for different drugs. It cannot be assumed that short-term or even single-dose trials pose no risk to patients and healthy volunteers. Even single doses of certain drugs used in challenge studies in vulnerable populations have been shown to induce suicidality. Treatment-emergent suicidality has also been reported in short-term phase 1 studies in healthy volunteers with several different antidepressants. Suicidality assessments should, therefore, be included even in single-dose trials.

b. Microdose trials

It is reasonable to omit suicidality assessments in microdose studies involving single, low doses that are not expected to have any measurable pharmacological effects. Such doses are typically used in imaging studies exploring receptor occupancy.

4. Timing of Assessments

In general, suicidality assessments should be conducted at baseline and at all planned visits at which other clinical assessments are to be carried out in a study for which suicidality assessments are considered appropriate. For certain drugs (e.g., those with particularly long elimination half-lives), it may make sense to include follow-up assessments even after dosing has stopped. These assessments should also be conducted at any unplanned visits at which other clinical assessments are needed.

Determining what constitutes a visit is generally straightforward for an outpatient study, but not necessarily for an inpatient study. For an inpatient study, suicidality assessments would ordinarily be done at the same times as other clinical assessments. Sponsors should seek advice from the FDA if there are questions about the appropriate frequency and timing of assessments for particular studies.

5. Implementation During Ongoing Trials

Determining how to implement suicidality assessments in ongoing trials may involve some discussion with the FDA. Suicidality data derived from a trial in which suicidality assessments were added after the trial was well along would not be optimal for inclusion in a meta-analysis. Nevertheless, it may still be important to add suicidality assessments for the protection of patients involved in the ongoing trial. For a trial that is close to completion, it would not be feasible to go through the formal process of amending the protocol and obtaining investigational review board concurrence. Nevertheless, even in these instances, it may be useful to alert investigative sites of the general concern about possible drug-induced suicidality, so they can individually decide how to address this issue.

IV. PROSPECTIVE ASSESSMENT OF SUICIDALITY OCCURRENCE — SPECIFIC INDICATION RECOMMENDATIONS

As noted, although past experience indicates that assessment of suicidality should be a regular part of development programs involving antidepressants and antiepileptic drugs, the heightened risk of suicide in most psychiatric illnesses suggests that suicidality should be assessed as part of the evaluation of any drug being developed for a psychiatric condition (i.e., those indications managed in the Division of Psychiatry Products). There are no data to support the view that patients with nondepressed psychiatric disorders have any lesser vulnerability to treatment-induced suicidality than patients with overt depression. If anything, based on limited exploratory analyses of the adult antidepressant data, the risk may be greater in nondepressed psychiatric patients.[9] Moreover, in the meta-analysis for suicidality with antiepileptic drugs, the odds ratio for suicidality was greater for epilepsy patients than it was for the psychiatric patients treated with these drugs, even though the absolute rates were higher in psychiatric patients compared to epilepsy patients.[10] Therefore, other than the exceptions noted in section III.C., prospective suicidality assessments should be carried out in all clinical trials involving any drugs being developed for any psychiatric indications, as well as for all antiepileptic drugs and other neurologic drugs with central nervous system (CNS) activity, both inpatient and outpatient, including phase 1 trials involving healthy volunteers.

Tempting as it may be to think that patients without a psychiatric condition receiving nonpsychiatric drugs would not be at risk for drug-induced suicidality, experience suggests that this belief may be erroneous. Although there are few controlled trial data in these settings, there has been long-standing concern about a variety of drugs, including isotretinoin and other tretinoins, beta blockers (especially those entering the brain), reserpine, drugs for smoking cessation, and drugs for weight loss, for which possible signals of risk for suicidality have already been identified. Therefore, we recommend that prospective suicidality assessments be

[9] Stone, M, T Laughren, ML Jones, M Levenson, PC Holland, A Hughes, TA Hammad, R Temple, and G Rochester, 2009, Risk of Suicidality in Clinical Trials of Antidepressants in Adults: Analysis of Proprietary Data Submitted to U.S. Food and Drug Administration, BMJ, 339:b2880.

[10] FDA, 2008, FDA Advisory: Suicidality and Antiepileptic Drugs (http://www.fda.gov/cder/drug/Infopage/antiepileptics/default.htm).

carried out in all clinical trials for all drugs that are pharmacologically similar to drugs in the above list. Assessments should be conducted in both inpatient and outpatient trials, and even phase 1 trials involving healthy volunteers, with the exceptions noted in section III.C. This list of suspect drugs will expand as new possible signals are detected. One of the advantages of conducting suicidality assessments more broadly is that future meta-analyses may either confirm the signal, or provide reassurance that the signal is not real.

The possibility that suicidality assessments should be conducted as part of essentially all drug development programs, even for drugs not yet recognized as having CNS effects, has also been considered, but this guidance is not recommending that approach. Further experience may change our view on this issue and comments on this current recommended approach are welcome.

APPENDIX A: C-CASA CODES AND DEFINITIONS[11]

Completed Suicide

A self-injurious behavior that resulted in fatality and was associated with at least some intent to die as a result of the act.

Suicide Attempt

A potentially self-injurious behavior, associated with at least some intent to die, as a result of the act. Evidence that the individual intended to kill him- or herself, at least to some degree, can be explicit or inferred from the behavior or circumstance. A suicide attempt may or may not result in actual injury.

Preparatory Actions Toward Imminent Suicidal Behavior

The individual takes steps to injure him- or herself, but is stopped by self or others from starting the self-injurious act before the potential for harm has begun.

Suicidal Ideation

Passive thoughts about wanting to be dead or active thoughts about killing oneself, not accompanied by preparatory behavior. If ideation is deemed inherently related to a behavioral act, a separate rating is not given. However, if there is no clear relationship to a behavioral event, a separate classification of ideation is warranted.

Self-Injurious Behavior Intent Unknown

Self-injurious behavior where associated intent to die is unknown and cannot be inferred. The injury or potential for injury is clear, but why the individual engaged in that behavior is unclear.

Fatal Event: Not Enough Information

Death where there is insufficient information to determine whether the event involved deliberate suicidal behavior or ideation. There is reason to suspect the possibility of suicidality but not enough to be confident that the event was not something other, such as an accident or psychiatric symptom. An injury sustained on a place on the body consistent with deliberate self-harm or suicidal behavior (e.g., wrists), without any information as to how the injury was received, would warrant placement in this category.

[11] Posner, K, MA Oquendo, M Gould, B Stanley, and M Davies, 2007, Columbia Classification Algorithm of Suicide Assessment (C-CASA): Classification of Suicidal Events in the FDA's Pediatric Suicidal Risk Analysis of Antidepressants, Am J Psychiatry, 164:1035-1043.

Self-Injurious Behavior Without Suicidal Intent

Self-injurious behavior associated with no intent to die. The behavior is intended purely for other reasons, either to relieve distress (often referred to as *self-mutilation* (e.g., superficial cuts or scratches, hitting or banging, or burns)) or to effect change in others or the environment.

Other (Accident, Psychiatric, Medical)

No evidence of any suicidality or deliberate self-injurious behavior associated with the event. The event is characterized as an accidental injury, psychiatric or behavioral symptoms only, or medical symptoms or procedure only.

Nonfatal Event: Not Enough Information

Nonfatal event where there is insufficient information to determine whether the event involved deliberate suicidal behavior or ideation. There is reason to suspect the possibility of suicidality but not enough to be confident that the event was not something other, such as an accident or psychiatric symptom. An injury sustained on a place on the body consistent with deliberate self-harm or suicidal behavior (e.g., wrists), without any information as to how the injury was received, would warrant placement in this category.

APPENDIX B: SUICIDALITY DATA CODING FORM

Suicidality Data Coding Form

Study Number:
Patient Number:
Visit Number:
Visit Date:

Instructions

This form can be used for coding data obtained from studies involving prospective assessment of suicidality using an assessment instrument recommended by the FDA for this purpose (see the draft guidance for industry *Suicidality: Prospective Assessment of Occurrence in Clinical Trials*).[12] As indicated in the draft guidance, the instrument can be used to code the events at the time of assessment, and this coding summary form is intended to summarize the pertinent data for subsequent meta-analyses. As prospective assessment instruments for suicidality are created, some of these codes will become irrelevant for patients who can be assessed, in particular codes 5, 6, 8, and 9. Thus, summary data should be captured for only codes 1, 2, 3, 4, and 7. However, each coding term should have an indication, yes or no, regarding whether or not each particular term occurred at least once during the coding interval pertaining to the indicated visit. These terms are defined in the draft guidance, and a proposed algorithm for mapping assessments to these C-CASA codes is provided.

Event Code	Yes	No
(1) Completed Suicide		
(2) Suicide Attempt		
(3) Preparatory Actions Toward Imminent Suicidal Behavior		
(4) Suicidal Ideation		
(7) Self-Injurious Behavior Without Suicidal Intent		

[12] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.