# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 125370

# CROSS DISCIPLINE TEAM LEADER REVIEW

# Cross-Discipline Team Leader Review

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| **Date** | February 17, 2011 |
| **From** | Sarah (Okada) Yim, M.D. |
| **Subject** | Cross-Discipline Team Leader Review |
| **NDA/BLA # Supplement#** | 125370/0 |
| **Applicant** | Human Genome Sciences |
| **Date of Submission** | June 9, 2010 |
| **PDUFA Goal Date** | December 9, 2010, Amendment Ext. to March 10, 2011 |
| | |
| **Proprietary Name / Established (USAN) names** | Benlysta®/Belimumab |
| **Dosage forms / Strength** | 120 mg lyophilized/5 ml vial, 400 mg lyophilized/20 ml vial |
| **Proposed Indication(s)** | 1. (b) (4) adult patients with active, autoantibody-positive systemic lupus erythematosus who are receiving standard therapy. |
| **Recommended:** | *Approval, with revisions to proposed label* |

## 1. Introduction

Belimumab is a human IgG1λ monoclonal antibody (mAb) targeting the novel target ligand B lymphocyte stimulator (BLyS), also known as B cell Activating Factor belonging to the TNF Family (BAFF), and intended for the treatment of systemic lupus erythematosus (SLE). This ligand plays a role in B cell selection and survival. It is expressed as a cell surface trimer, which is cleaved to become the soluble circulating form that is bound by belimumab. Thus belimumab works to prevent soluble BLyS/BAFF from binding to its three receptors (see Figure 1 below).

This biologic license application (BLA) is based upon two studies with very similar protocols: HGS1006-C1056 (n=819) and HGS1006-C1057 (n=810). These studies utilized an identical study design but differed in duration of treatment (76 weeks for Study 1056 and 52 weeks for Study 1057) and geographic region (primarily US and Europe for Study 1056 and primarily Asia and Latin America for Study 1057). Both studies used a novel composite endpoint—the SLE Responder Index—as primary endpoint at Week 52, but were very different in terms of results. This difference between studies raised questions about the generalizability of study results across SLE populations.

Results for secondary endpoints and other exploratory analyses also raised questions regarding the extent and limitations of belimumab's treatment effect. Describing belimumab's treatment effect proved to be difficult given the variability in the study data and the often small

subgroups upon which observations could be made. The most certainty regarding treatment effects was limited to the most common manifestations in the trials—mucocutaneous and musculoskeletal. As will be discussed in greater detail below, these efficacy issues, and the relative safety profile of belimumab, were considered in the context of the unmet medical need for approved therapies in SLE.

## 2. Background

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. 20-30% in patients of European descent) and the disease is more severe. High rates (60-70%) 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]

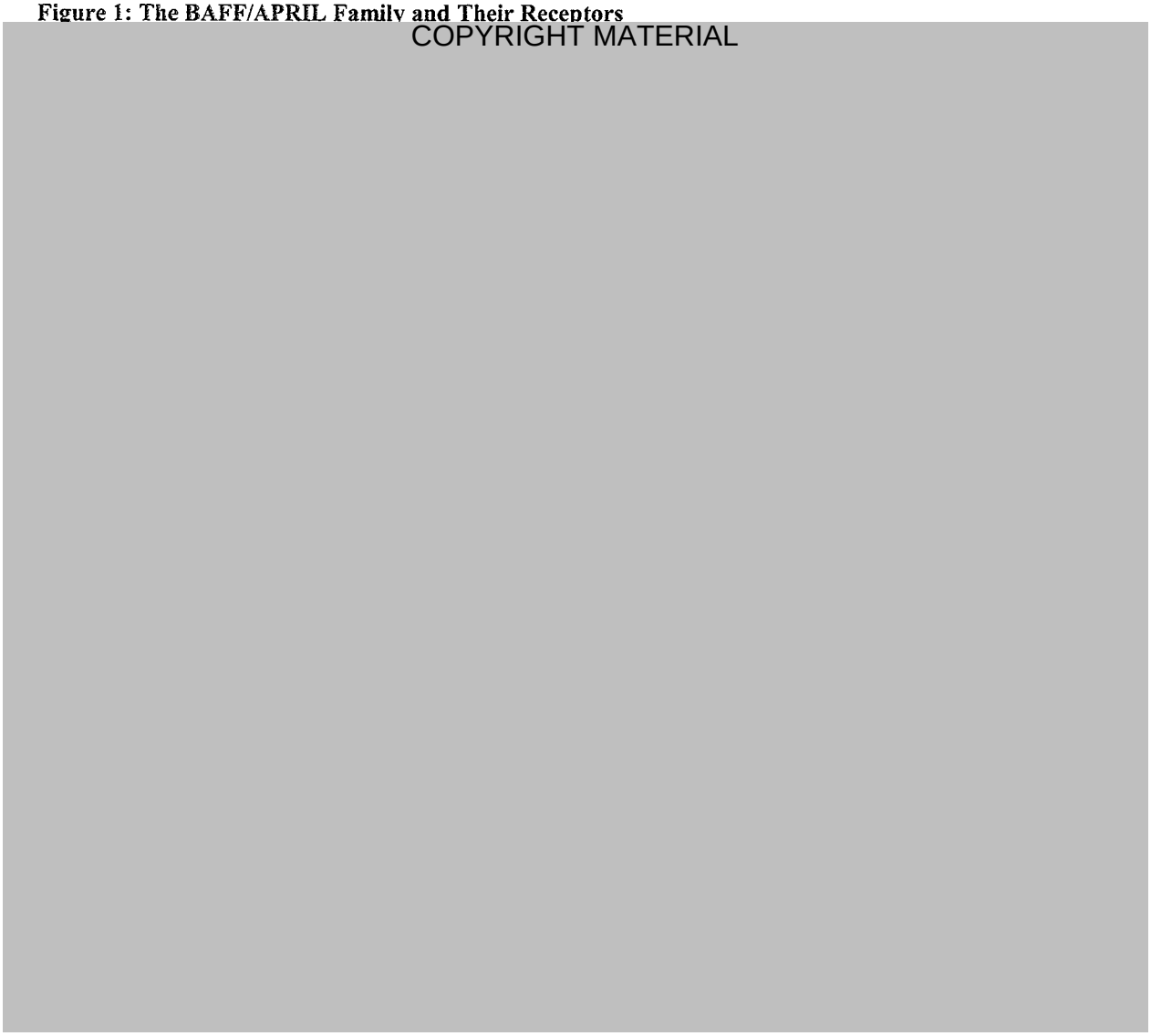
Although a number of treatments have been studied in SLE, only 3 products have been approved for this indication thus far: corticosteroids, hydroxychloroquine, and aspirin. Thus the majority of immunosuppressive medications used routinely in the treatment of SLE are used off-label. Because SLE is a disorder characterized by production of multiple autoantibodies, it has long been hypothesized that autoreactive B cells are a key pathogenic entity. Therefore B-cell directed therapy, such as the B-cell depleting anti-CD20 mAb rituximab would be considered a rational treatment option. Unfortunately, controlled trials of rituximab in non-renal lupus (EXPLORER)[3] and lupus nephritis (LUNAR) have not been successful at demonstrating a treatment difference between rituximab and control group treatment. In stark contrast to the controlled trial results, there exists a growing body of clinical experience that speaks to rituximab's efficacy for refractory SLE manifestations. This apparent paradox raises the question—does B-cell directed therapy really not work for SLE, or is there something about the way it is being studied in controlled trials that prevents the treatment effect from being evident? The belimumab trials were another test of this question—with a failed Phase 2 study available to inform the design of the Phase 3 trials and primary endpoint.

Belimumab is a human monoclonal antibody targeting soluble BLyS/BAFF. BLyS/BAFF is a member of the TNF superfamily that appears to support naïve B cell survival, influences B cell selection, and during antigen activation upregulates TLR expression, B cell survival and

[1] Pons-Estel et al. Semin Arthritis Rheum 2010 Feb ; 39:257-268
[2] Borchers et al. Autoimmunity Reviews 9 (2010):A277-A287
[3] Merrill et al. Arthritis & Rheum Jan 2010; 62(1):222-233

promotes Ig class switching. As shown in Figure 1 below, BLyS/BAFF shares some receptors in common with APRIL (TACI and BCMA), but is a sole ligand for the BAFF-receptor (BAFF-R).

**Figure 1: The BAFF/APRIL Family and Their Receptors**




*Source: Davidson, Current Opinion in Immunology 2010, 22:1-8.*

# 3. CMC/Device

*Primary Product Quality Reviewer: Sean Fitzsimmons, Ph.D.*
*Product Quality Team Leader: Marjorie Shapiro, Ph.D.*
*The following section was excerpted/adapted from Dr. Shapiro's review.*

- **General product quality considerations**

Belimumab is a human IgGl, lambda first-in class therapeutic monoclonal antibody specific for B lymphocyte stimulator (BLyS; BAFF) that binds to soluble BLyS with high affinity (267 ± 70 pM). It does not bind to membrane-bound BLyS (assessed by flow cytometry). Belimumab was derived from a phage display library generated by amplification of the VH, $V_{kappa}$ and $V_{lambda}$ transcripts from B cells pooled from 43 healthy donors and screened for binding to recombinant BLyS. The selected clone was reverse engineered to produce the full length IgG1 heavy chain and full length lambda light chain. Belimumab has a typical antibody structure, composed of two identical H chains and two identical L chains, with a molecular weight of ~147 kDa.

Belimumab is expressed in an NSO mouse myeloma cell line and manufactured using typical bioreactor and purification methods for therapeutic monoclonal antibodies. There have been multiple comparability studies during the course of clinical development of belimumab for both drug substance and drug product. Pre-clinical and phase 1 studies used belimumab drug substance manufactured by the (b) (4)) and (b) (4)) processes. Phase two studies used the (b) (4)) process. Phase 3 studies used the (b) (4) processes. The (b) (4) process is the proposed commercial process. Comparability was adequately demonstrated for each drug substance process change (and resulting drug product).

Belimumab drug product is supplied as a sterile, preservative-free lyophilized powder for reconstitution, dilution, and intravenous infusion provided in single-use glass vials with a latex-free rubber stopper and a flip- off seal. Any unused portion of the vial must be discarded. There are two drug product dosage forms; a 120 mg vial (5 mL) and a 400 mg vial (20 mL). The batch formula (b) (4) is: 80 g belimumab, 0.16 g citric acid monohydrate, 2.7 g sodium citrate dihydrate, (b) (4); sucrose, 0.4 g polysorbate 80 and WFI (b) (4). Belimumab drug product is reconstituted with sterile Water for Injection (WFI) that is not supplied or packaged with the belimumab drug product.

The belimumab drug product overfill is (b) (4), and (b) (4), for the 120 mg and 400 mg vial configurations, respectively. The overfill amount was calculated based on the USP and Ph. Eur. recommended excess volume. The overfill amounts allow for reconstitution volumes of 1.5 and 4.8 mL, which can be accurately measured using 3 and 5 mL syringes with minor graduations, respectively.

Both the 5 mL and 20 mL vials are USP and (b) (4) Type I glass, (b) (4) tubing. Stoppers for both vial sizes are 20 mm, (b) (4) gray, (b) (4) rubber, lyophilization stopper; (b) (4) (b) (4) Seals are aluminum, 20 mm, white, flip-off (400 mg/vial) or aluminum, 20 mm, dark gray, flip-off (120 mg/vial). Belimumab drug substance is formulated in (b) (4) sodium citrate, (b) (4) sucrose, (b) (4) polysorbate 80, pH 6.5, at a concentration of (b) (4) belimumab/L.

Adequate data were provided for the proposed expiration dating of Benlysta® drug product of 36 months for both 120 and 400 mg vial configurations from the time of production when stored at 2-8°C. The stability of belimumab during in-use periods was supported by post-

reconstitution studies where samples were incubated for 8 hours at 2-8°C (upright and inverted positions). Belimumab drug product does not contain a preservative. Vials are single use.

- **Facilities review/inspection**

The drug substance manufacturing facility, Human Genome Sciences, Inc., Rockville MD (FEI=1000303703) was inspected on 9/7-10/2010 by CDER inspectors and found to be acceptable from a CGMP perspective.

The inspection of the drug product facility, (b) (4) was waived because this facility was inspected on 4/12-16/2010 and is in compliance with CGMPs.

- **Other notable issues (resolved or outstanding)**

Product quality Post Marketing Requirement:

**1. Develop improved immunogenicity assays. The Agency provided the following clarification on 31 January 2011: The limits of detection of the immunogenicity assays (screening, confirmatory and neutralizing) are all variably sensitive to product interference, such that patients with product levels above certain interference thresholds for each assay will not yield interpretable results. We recommend that you develop assays that are less sensitive to product interference that are capable of detecting HAHA, in the presence of belimumab, at ranges that would be expected to occur in patients receiving both the high and low doses.**

Final Protocol Submission Date: March 2012 (PAS)
Study/Clinical Trial Completion Date: Not applicable
Final Report Submission Date: January 2013 (CBE-30)

Product quality Post Marketing Commitments:

1. **Submit data supporting microbial control for the (b) (4) lifetime studies in a CBE-0 supplement by June 2012.**

Final Protocol Submission Date: 09/24/2010 (SN 0005)
Study/Clinical Trial Completion Date: 12/30/2011
Final Report Submission Date: 06/30/2012

2. **Qualify the capper and validate the integrity of the belimumab drug product container closure in a helium leak test using 5 mL vials prepared at minimum and maximum sealing forces. Information and summary validation data of the helium leak test and the integrity of the belimumab drug product container closure should be submitted in a Changes Being Effected (CBE-0) supplement by June 30, 2011. Include the preparation of the positive controls and sensitivity (breach size) of the helium leak test.**

Final Protocol Submission Date: 03/31/2011
Study/Clinical Trial Completion Date: 04/29/2011
Final Report Submission Date: 06/30/2011

3. **Provide quantitative data to demonstrate** (b) (4) **The quantitative qualification data should be submitted in a Changes Being Effected (CBE-0) supplement by June 30, 2011.**

Final Protocol Submission Date: 03/31/2011
Study/Clinical Trial Completion Date: 04/29/2011
Final Report Submission Date: 06/30/2011

(b) (4)

# 4. Nonclinical Pharmacology/Toxicology

*Primary pharmacology/toxicology reviewer: Mamata De, Ph.D.*
*Pharmacology/toxicology supervisor: Molly Topper, Ph.D.*

- **General nonclinical pharmacology/toxicology considerations**

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.

- **Carcinogenicity**

Carcinogenicity studies were not performed.

- **Reproductive toxicology**

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 and 0 infants), low (6 fetus and 2 infants), and high dose group (3 fetus and 1 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.

- **Other notable issues (resolved or outstanding)**

Not applicable.

# 5. Clinical Pharmacology/Biopharmaceutics

*Primary clinical pharmacology reviewer: Ping Ji, Ph.D.*
*Clinical pharmacology supervisor: Yun Xu, Ph.D.*

- **General clinical pharmacology/biopharmaceutics considerations**

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.

*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 a positive immunogenicity response did not appear to affect belimumab PK.

- **Drug-drug interactions**

No formal drug-drug interaction studies were performed with belimumab.

- **Pathway of elimination**

Belimumab is an antibody, and is therefore subject to clearance by the reticuloendothelial system.

- **Intrinsic factors: age, gender, hepatic insufficiency and renal impairment**

*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.

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

- **Demographic interactions/special populations**

*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.

*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.

- **Thorough QT study or other QT assessment**

As a macromolecule, belimumab would not be expected to affect the cardiac conduction system. A thorough QT study was neither required nor submitted.

- **Other notable issues (resolved or outstanding)**

None.

# 6. Clinical Microbiology

Not applicable.

# 7. Clinical/Statistical- Efficacy

*Primary Clinical Reviewer: Rosemarie Neuner, M.D., M.P.H*
*Primary Statistical Reviewer: Ruthanna Davi, Ph.D.*
*Statistical Team Leader: Joan Buenconsejo, Ph.D.*

*Description of Efficacy Variables*

There are a variety of SLE disease activity outcome measures, each with slightly different characteristics. Most of these outcome measures have been validated in the setting of long-term observational studies rather than randomized controlled trials. Thus the optimal outcome measure for SLE clinical trials has not yet been identified. As discussed below, the Applicant utilized a novel composite endpoint, the SLE Responder Index (SRI), for the pivotal studies 1056 and 1057. This endpoint was comprised of 3 components—the SELENA-SLEDAI, the BILAG, and the Physician's Global Assessment.

The SLEDAI 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.[4] A clinically meaningful difference has been reported to be improvement of

[4] Abrahamowicz et al. J Rheumatol 1998; 25(2):277-284

6 points or worsening of 8 points.[5] 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. The SELENA-SLEDAI was the index used in the belimumab pivotal trials.

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 (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.

The Physician's Global Assessment is simply a subjective rating by a single assessor on a visual analog scale ranging from 0 to 10, with 0 being no disease activity and 10 being the most severe disease activity.

Exploratory analyses done on the data from the failed Phase 2 Study LBSL02 served to inform the development of the SRI, a novel endpoint created based on exploratory analyses of its data. This endpoint was intended to capture clinically meaningful change yet ensure that there would not be significant worsening in overall disease activity. Using this composite index, a patient is defined as a responder if they have:

- a $\geq$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 or 2 new BILAG B organ domain scores at the time of the primary endpoint assessment (i.e. Week 52) compared to baseline.

A four point reduction in the SELENA-SLEDAI score was selected on the basis of some cohort studies that suggest this increment is clinically meaningful[6]; however other cohort studies have suggested a 7 point improvement is the minimum clinically important difference[7].

*Summary of the Clinical Development Program*

Belimumab administered as an IV infusion in subjects with SLE has been studied in one Phase 1 trial (LBSL01) testing single and repeat (x 1) dosing in 70 SLE patients, one Phase 2 randomized, double-blind, placebo-controlled trial (LBSL02) of 52 weeks duration in 449 SLE

[5] ACR Ad Hoc Committee on SLE Response Criteria, Arthritis & Rheum, November 2004, 50(11):3418-3426
[6] Furie et al., Arthritis Care & Research, September 2009; 61(9):1143-1151
[7] ACR Ad Hoc Committee on SLE Response Criteria, Arthritis & Rheum, November 2004, 50(11):3418-3426

patients, and two Phase 3 randomized, double-blind, placebo-controlled trials (C1056 and C1057) of 76 and 52 week duration, respectively, with trial populations of 819 and 865 SLE patients, respectively. (b) (4)

Four doses were tested in single and 2-time dosing in LBSL01—1 mg/kg, 4 mg/kg, 10 mg/kg and 20 mg/kg. Results from this trial were not submitted to the BLA; however the 20 mg/kg dose was dropped for the next study, which was the large Phase 2 trial LBSL02. The primary endpoints for the Study LBSL02 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 antidsDNA), which represented 72% of the study population. Thus only autoantibody positive SLE patients were studied in the two pivotal trials 1056 and 1057.

Studies 1056 and 1057 had identical protocols, with the same primary endpoint of SRI at Week 52; however Study 1056 had a longer controlled period of 76 weeks to assess for possible delayed treatment effect in case no effect was seen at the Week 52 timepoint. Both Study 1056 and Study 1057 enrolled patients with active, seropositive SLE on stable immunosuppressive medications. 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 SELENA 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.

Study 1056 enrolled 819 patients primarily in North America (65 centers) and Europe (62 centers). The remaining 9 centers were in Latin America. Study 1057 enrolled 810 SLE patients from outside the US, primarily in Asia (41 centers) and Latin America (38 centers). The remaining 11 centers were in Europe. As will be discussed further below, the most robust efficacy results were noted in Study 1057. Some possibly relevant differences were noted between the two studies in terms of population, age, and disease characteristics. As shown in Table 1 below, the study populations differed, with Study 1056 being approximately 70% Caucasian whereas the Study 1057 population was 1/3 Asian, 1/3 Native American (including indigenous people of Latin America) and almost 1/3 Caucasian. Other notable differences include a skew toward a younger population, shorter disease duration, more baseline BILAG A

disease activity, less baseline damage (as assessed by the SLICC), higher corticosteroid usage and lower use of other immunosuppressives in Study 1057. There was also a higher proportion of patients with proteinuria and low complement in Study 1057.

**Table 1: Selected Baseline Differences between Studies 1056 and 1057**

| Selected Baseline Differences Between the Two Phase 3 Trials | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Trial 1056 | | | | Trial 1057 | | | |
| | Placebo n = 275 | 1 mg/kg n = 271 | 10 mg/kg n = 273 | All n = 819 | Placebo n = 287 | 1 mg/kg n = 288 | 10 mg/kg n = 290 | All n = 865 |
| Race | | | | | | | | |
| White/Caucasian | 188 (68) | 192 (71) | 189 (69) | 569 (70) | 82 (29) | 76 (26) | 71 (24) | 821 (26) |
| Asian | 11 (4) | 6 (2) | 11 (4) | 28 (3) | 105 (37) | 106 (37) | 116 (40) | 327 (38) |
| Black/African | 39 (14) | 40 (15) | 39 (14) | 118 (14) | 11 (4) | 8 (3) | 11 (4) | 30 (3) |
| Native American | 36 (13) | 33 (12) | 34 (12) | 103 (13) | 89 (31) | 98 (34) | 92 (32) | 279 (32) |
| Pacific Islander | 1 (0.4) | 0 | 0 | 1 (0.1) | 0 | 0 | 0 | 0 |
| Multiracial | 2 (1) | 3 (1) | 3 (1) | 8 (1) | 1 (0.3) | 3 (1) | 1 (0.3) | 5 (0.6) |
| Hispanic/Latino | 55 (20) | 62 (23) | 56 (21) | 173 (21) | 143 (50) | 141 (49) | 136 (47) | 420 (49) |
| Age | | | | | | | | |
| ≤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 | 9 (3) | 4 (1) | 3 (1) | 16 (2) | 5 (2) | 4 (1) | 2 (1) | 11 (1) |
| SLE disease duration | | | | | | | | |
| Mean (SD) | 7.4 (6.7) | 7.9 (7.1) | 7.2 (7.4) | 7.5 (7.1) | 5.9 (6.1) | 5.0 (4.6) | 5.0 (5.0) | 5.3 (5.3) |
| BILAG activity | | | | | | | | |
| At least 1A | 37 (14) | 38 (14) | 24 (9) | 99 (12) | 52 (18) | 58 (20) | 54 (19) | 164 (19) |
| At least 1A or 2B | 187 (68) | 173 (64) | 160 (59) | 520 (64) | 166 (58) | 166 (58) | 172 (59) | 504 (58) |
| SLICC Damage Index | | | | | | | | |
| Mean (SD) | 0.99 (1.45) | 1.04 (1.39) | 0.94 (1.38) | 0.99 (1.41) | 0.55 (0.93) | 0.60 (1.06) | 0.55 (1.00) | 0.57 (1.00) |
| Proteinuria | | | | | | | | |
| > 2 g/24 hrs | 11 (4) | 7 (3) | 15 (5) | 33 (4) | 21 (7) | 26 (9) | 19 (7) | 66 (8) |
| Low complement | | | | | | | | |
| Low C3 | 116 (42) | 100 (37) | 115 (42) | 331 (40) | 132 (46) | 148 (51) | 147 (51) | 427 (49) |
| Low C4 | 143 (52) | 141 (52) | 147 (54) | 431 (53) | 160 (56) | 173 (60) | 180 (62) | 513 (59) |
| Baseline steroid use | | | | | | | | |
| Any use | 212 (77) | 211 (78) | 200 (73) | 623 (76) | 276 (96) | 276 (96) | 278 (96) | 830 (96) |
| >7.5 mg/day | 126 (46) | 130 (48) | 120 (44) | 376 (46) | 192 (67) | 204 (71) | 204 (70) | 600 (69) |
| Baseline Immunosuppressives | | | | | | | | |
| Any use | 154 (56) | 153 (56) | 148 (54) | 455 (56) | 122 (42) | 120 (42) | 123 (42) | 365 (42) |

Sources: Tables 2.7.3-14, 2.7.3-16, 2.7.3-17, and 2.7.3-18 from Module 2.7.3 Summary of Clinical Efficacy

With respect to baseline organ system involvement, the primary difference between the two studies was a much larger proportion of patients with musculoskeletal system involvement in Study 1056. There is also almost double the proportion of patients with stable renal involvement in Study 1057, although this is still a relatively small proportion of the overall patient population, at 13%. The prevalence of individual organ systems involved in study patients in both studies was different than background rates in the SLE population; specifically, neurological and renal manifestations were uncommon in the studies because patients with active neurologic or renal manifestations were excluded.

**Table 2 BILAG A or B Organ Domain Involvement at Baseline**

| 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%)** |
| Reual | | | | | | | | |
| 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%)** |

Source: Table T20 of Summary of Clinical Efficacy Appendices

The efficacy results that follow should be interpreted with the aforementioned differences between Studies 1056 and 1057 in mind.

*Primary Efficacy Endpoint*

As shown in Table 3 below, the proportion of patients experiencing an SRI response at Week 52 was higher in the belimumab 10 mg/kg treatment arms of both studies compared to the respective control arms. In Study 1057, overall responses (including the placebo add-on group) were higher, there was a larger difference between the 10 mg/kg group and placebo, and a dose-related increase in the proportion of responders was noted. In contrast, results of Study 1056 only reached a statistically significant difference between the 10 mg/kg group and placebo, and there was not a large difference in the proportion of responders between the 1 mg/kg and 10 mg/kg group. There was a numerically greater proportion of patients meeting criteria for each of the components of the SRI in the belimumab groups of both studies; however results were more robust in Study 1057. For Study 1056, the result for the SELENA-SLEDAI component is driving the efficacy result for the 10 mg/kg group, which did not exhibit a statistically significant improvement for the other SRI components. In fact, the 1 mg/kg group had better results than for the 10 mg/kg group for those SRI components.

**Table 3: Proportion of Patients with an SRI Response at Week 52**

| | 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)

The applicant also provided analyses of the SRI response using higher SELENA-SLEDAI point reductions (Table 2.7.3-28 of Applicant's Summary of Clinical Efficacy). For both studies, increasing the point-reduction thresholds increased the difference between belimumab treatment and placebo-add-on treatment. For example, for an SRI using a 7 point reduction in the SELENA-SLEDAI as a threshold, 29/275 (10.5%) of placebo-treated patients achieved a response compared to 42/271 (15.5%) of patients on belimumab 1 mg/kg and 46/273 (16.8%) of patients on belimumab 10 mg/kg. The actual number of patients eligible to achieve such a reduction (i.e. score ≥7 at baseline) was 216 in the placebo group and 217 in each of the belimumab groups.

*Subgroup analyses*

To further explore the apparent difference in results between Study 1056 and Study 1057, efficacy results were evaluated by subgroups based on region and selected baseline characteristics. As shown in Table 4 below, although the belimumab groups of Study 1056 had a slightly higher proportion of SRI responders than the placebo group, the difference is small in the subgroup of patients in the USA/Canada region (highlighted). Findings in the sponsor-combined racial subgroup of African or indigenous American descent (also highlighted in Table 4) are remarkable in that the two trials showed conflicting results. This apparent discrepancy was due to conflicting results in the Alaska native or American Indian subgroup between the two trials. Demographic data were not provided with sufficient granularity to explore what the difference in this subgrouping might be between the two

studies; although it is unlikely that Alaska natives were enrolled in Trial 1057. With the caveat that the black/African subgroup in Trial 1057 were very small, results for the black/African subgroup were consistent between the two studies—and suggested a reversal of effect, with a higher proportion of patients in the placebo groups achieving success on the SRI (see Table 5 below).

**Table 4: Proportion of SRI Responders by Region and Selected Baseline Characteristic Subgroups**

| | 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 (45%) | 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.

**Table 5: Proportion of SRI Responders by Racial Subgroups**

| 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.

*Other Efficacy Endpoints*

*SRI results at Week 76*

As mentioned previously, Study 1056 had a longer controlled period of 76 weeks to assess for possible delayed treatment effect in case no effect was seen at the Week 52 timepoint. When compared to Week 52 results (see Table 3 above), the proportion of SRI responders in all treatment groups dropped by Week 76, with the proportion in the placebo group changing less. Therefore the difference between the belimumab treatment groups and the placebo group was no longer statistically significant.

**Table 6: Proportion of SRI Responders at Week 76, 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 Prednisone*

The impact of belimumab on the concomitant steroid requirement in SLE was assessed as a secondary endpoint. In an attempt to define a clinically meaningful improvement, the endpoint was defined the proportion of patients with baseline steroid requirement greater than 7.5 mg/day (prednisone or equivalent) who were able to achieve a reduction of at least 25% from baseline to less than 7.5 mg/day during Week 40 through 52. Although there was a trend toward a higher of proportion of patients who were able to meet this level of reduction in the belimumab treatment groups compared to the placebo groups, results only achieved statistical significance for the 1 mg/kg group of Trial 1057.

**Table 7: 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.

*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 18]; or
2) New BILAG A organ domain score or 2 new BILAG B organ domain scores compared with baseline.

**Table 8: SELENA Trial Definition of SLE Flares**



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

Table 9 displays the results from the flare analyses assessed by the modified SLE Flare Index. With respect to risk of any flare, the reduction in risk with belimumab treatment was significant only in Study 1057. 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 significantly longer as compared to placebo (84 days). In Study 1056, the risk for having a severe disease flare over 52 weeks was significantly reduced only in the 1 mg/kg belimumab group, whereas in Study 1057 the risk was significantly reduced only in the 10 mg/kg belimumab group. Although results were not always statistically significant, numerically, the results suggest there may be a treatment benefit of belimumab with respect to flares. Results from Weeks 24 to 52, the period during which changes in background medications were restricted, were consistent with the overall results (data not shown).

**Table 9: Modified SELENA-SLEDAI Flare Index 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 risk for flare was also assessed with respect to BILAG flares. Similarly, a statistically significant reduction in risk for developing a BILAG 1A/2B organ domain flare over 52 weeks was observed primarily in Trial 1057, as shown in Table 10 below.

**Table 10: 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.

*Improving 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 8 organ systems similar to BILAG organ domains for exploratory analyses. The proportion of patients with involvement of any given organ system was small with the exception of the mucocutaneous (alopecia, mucosal ulcers, and rash), immunology (anti-dsDNA and low complement), and musculoskeletal (arthritis and myositis) organ systems. For these three organ system subgroups, the proportion of patients improving trended higher in the belimumab groups of Studies 1056 and 1057. With respect to new organ involvement, 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.

Using BILAG organ domains to assess improvement, a similar trend in favor of belimumab for most organ domains was observed, with the exception of the cardiorespiratory subgroup in Study 1057 and the vasculitis subgroup of Study 1056. However, the proportion of patients

experiencing worsening in BILAG organ domain scores was similar among all three treatment groups of each study.

*SLICC Damage Index*

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 11, there were no consistent or significant differences between the three treatment groups in either study with respect to progression in the damage index.

**Table 11: 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

- **Summary of statistical reviewer review and the clinical efficacy review with explanation for CDTL's conclusions and ways that any disagreements were addressed**

The statistical and clinical teams were in agreement regarding the interpretation of efficacy findings as noted in the next section.

- **Notable efficacy issues both resolved and outstanding**

There are a number of findings in these studies that 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, SLE Flares.
- Lack of statistical significance for Responder Index results at Week 76 (Study 1056)
- 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
- Lack of consistency between studies—e.g. reduction in BILAG flares, 10 mg/kg increased time to BILAG flare in Study 1057 but not Study 1056; change in PGA—1 mg/kg better in Study 1056 and 10 mg/kg better in Study 1057; effect in the Native American subgroup—favorable in Study 1057, unfavorable in Study 1056.
- Lack of efficacy for the African heritage subgroup of both studies

However, results for the belimumab 10 mg/kg group of Studies 1056 and 1057 were consistent in demonstrating a statistically significant increase in the proportion of 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. Additionally, 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. 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.

# 8. Safety

- **Adequacy of the database, major findings/signals, special studies, foreign marketing experience, if any, and plans for postmarketing**

A total of 2578 subjects participated in the belimumab clinical development program, with 2272 having received treatment with belimumab. The majority of subjects were enrolled in IV belimumab SLE studies (2203 patients) with smaller numbers in the IV RA studies (283 patients) and 92 subjects in 2 studies of subcutaneous treatment. The primary safety population is comprised of the 2133 patients in Study LBSL02 and its long term extension LBSL99 (449 patients) and the two Phase 3 studies 1056 (819 patients) and 1057 (865 patients). Some safety analyses were provided for the "IV SLE studies," which includes patients in the primary safety population and the 70 SLE patients in the Phase 1 dose-ranging study LBSL01. In the IV SLE studies, approximately 1107 patients were treated with belimumab at any dose for at least 1 year and 1386 were treated for at least 6 months. Thus the number of patients and duration of exposure represented in the safety database are adequate to support the BLA.

Overall, the safety profile of belimumab appeared to be similar to the observed safety profile in the placebo add-on group in the controlled IV SLE studies (LBSL02, 1056, and 1057), although a relative increase in the observed rate of some important safety findings such as death and infection were noted in the belimumab groups compared to placebo. These imbalances will be explored further in a randomized, controlled safety study to be done postmarketing (see Section 13).

- **General discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests**

Table 12 below 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 proportion of patients in the listed categories were generally similar between treatment groups; however slightly more patients in the belimumab treatment groups experienced a serious adverse event (SAE), infection, serious infection, or death.

**Table 12: 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%) | 5 (0.7%) | -- | 6 (0.9%) | 11 (0.8%) |

Source: Table 2.7.4-8 of Summary of Clinical Safety

***Deaths***

There were a total of 14 deaths reported in the SLE controlled trials as follows: 4 patients died of cardiovascular (including stroke) events, 3 patients died of infectious etiologies, 2 patients died of respiratory arrest/failure, 2 patients committed suicide, 2 patients died of unknown causes and 1 patient died of a malignancy. Two of the subjects in the controlled studies (Subject CO0001-016 treated with placebo and Subject US041-013 treated with 10mg/kg of belimumab) whose deaths were attributed to cardiovascular and respiratory failure, respectively, were septic at the time of death, as was Subject TWO11-017 (pulmonary hemorrhage) from the ongoing extension study LBSL99. These deaths are consistent with the anticipated immunosuppressive effects of belimumab and an increase in risk for serious infections. Overall, the causes of deaths were consistent with expected etiologies of death related to underlying and concomitant medical conditions observed in these patient populations.

**Table 13: Exposure-Adjusted Incidence of Death in the IV SLE Controlled Studies**

| | 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 4-2; P. 25 of Appendix 4 of the Summary of Clinical Safety

However, it should be noted that while the absolute numbers of death in the clinical trials did not appear to be excessive, the exposure-adjusted incidence of death was approximately double in the belimumab treatment groups vs. the placebo treatment groups in the controlled period of the pooled IV SLE controlled studies, as shown in Table 13 above. Table 13 contains an additional death in a belimumab treatment group occurring outside the protocol-

specified window of attribution. If this death is removed, the exposure-adjusted incidence rate of death in the belimumab groups is 0.73/100 patient-years (95% CI 0.41, 1.29), thus the ratio of the rate in the belimumab groups vs. the placebo groups remained similar.

### *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 14, there were a total 9 confirmed malignancies reported during the controlled SLE trials. No discernable pattern for malignancies was observed.

**Table 14: 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%)[1]** | **3 (0.4%)[2]** | **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] | 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]Includes a patient diagnosed 62 days following last dose of study medications, which is outside the 8 week follow up period.
[2]Excludes Subject US052-000009 diagnosed with a thyroid neoplasm

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 (see Table 15, below).

**Table 15: Rate of Malignancy in the Studies LBSL02, 1056, and 1057**

| | Placebo | Belimumab | Rate Ratio |
|---|---|---|---|
| **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 | 0.91 |
| **95% Confidence Interval** | (0.09, 1.30) | (0.15, 0.89) | (0.19, 5.64) |
| **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 | 0.68 |
| **95% Confidence Interval** | (0.04, 1.07) | (0.04, 0.60) | (0.08, 8.20) |

[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 16 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 16: Malignancy Rates Excluding Non-Melanoma Skin Cancers for all Belimumab SLE Trials as of data cut-off date of December 31, 2009**

| | Background Rate[1] | Belimumab | Rate Ratio |
|---|---|---|---|
| **Number of Subjects** | 9547 | 1955 | |
| **Subject-Years** | 76,948 subject-years | 3507 subject-years | |
| **Subjects with Events** | 410 (4.3%) | 17 (0.9%) | 0.91 |
| **Malignancy Rate/100 Subject-Yrs (95% CI)** | 0.53 (0.48, 0.59) | 0.48 (0.28, 0.78) | (0.52, 1.47) |

[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.

A review of all cases of malignancy and neoplasms observed in the belimumab SLE safety database as of the cut-off date of December 31, 2009 revealed that 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.[8] However there was a numeric imbalance, with more cases occurring in the belimumab treatment arms.

*Serious Infections*

Because of its mechanism of action, belimumab would also be anticipated to increase the risk of infections, including serious infection. In fact, 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 17 below).

[8] 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 17: 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.

*Serious Adverse Events*

Table 18 is an abridged summary of the serious adverse events (SAE) observed during the controlled IV SLE studies. Overall, a slightly higher proportion of patients receiving belimumab treatment experienced SAE, compared to patients receiving placebo. The most common types of SAE were infections, followed by the gastrointestinal disorder and general disorder/administrative site condition system organ classes (SOC). A variety of other SAE were observed that would not generally be unexpected in the SLE patient population.

**Table 18: Serious Adverse Events Greater in Belimumab than Placebo 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 (1.8%)** | **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%) | 1 (0.1%) | 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 (0.9%) | 0 | 2 (0.1%) |
| Arteriosclerosis | 0 | 1 (0.1%) | 1 (0.9%) | 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

When assessed by Preferred Term, as in Table 19 below, pyrexia, urinary tract infection, lupus nephritis, cholelithiasis, cellulitis, and anemia were the most commonly observed SAEs in patients who received belimumab in the controlled IV SLE studies.

**Table 19: 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

### *Adverse Events Causing Discontinuation*

A similar proportion of patients experienced an adverse event leading to discontinuation in the belimumab treatment groups and the placebo group (see Table 20 below). The types of adverse events leading to discontinuation generally mirrored the overall pattern of events comprising serious adverse events.

**Table 20: 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%)** |

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

### *Common Adverse Events*

Most patients (>92%) in each treatment group experienced an adverse event during the controlled IV SLE trials. Infections were by far the most common manifestation, with 67% of placebo patients and 71% of belimumab-treated patients experiencing at least one infection in the IV SLE controlled studies LBSL02, 1056, and 1057. Table 21 lists the most common adverse event preferred terms reported by 5% or more patients in the combined belimumab groups of 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, diarrhea, fatigue, and back pain. The proportion of patients experiencing a given adverse event was generally similar across treatment arms, with the exception of the belimumab 4 mg/kg arm which contained only 111 patients (the dose was only used in Study LBSL02) and thus had larger incremental changes in proportions.

**Table 21: Common AEs, by Preferred Term, Occurring in >5% of Combined Belimumab Group of LBSL02, C1056, and C1057**

| 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 (5%) | 33 (5%) | 5 (5%) | 32 (5%) | 70 (5%) |

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

### *Laboratory Findings*

*Effect on Immunoglobulin Levels*

As shown in Table 22 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 of Module 2.7.4 Summary of Clinical Safety 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.

**Table 22: 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

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. Otherwise, no consistent effects of belimumab on hematology parameters were observed (Table 23 below).

**Table 23: Hematology Worst Toxicity Grades, IV SLE Controlled Studies LBSL02, 1056, and 1057**

| Worst Grade Observed | Placebo, n=675 | Belimumab 1 mg/kg, n = 673 | Belimumab 4 mg/kg, n = 111 | Belimumab 10 mg/kg, n = 674 |
|---|---|---|---|---|
| **Hemoglobin** | (n=674) | (n=668) | (n=110) | (n=672) |
| Grade 3, 6.5 - 8.0 g/dL | 30 (4.5%) | 21 (3.1%) | 4 (3.6%) | 9 (1.3%) |
| Grade 4, <6.5 g/dL | 2 (0.3%) | 3 (0.4%) | 1 (0.9%) | 1 (0.1%) |
| **Lymphocyte Count** | (n=674) | (n=668) | (n=110) | (n=672) |
| Grade 3, 200 to <500/mm3 | 155 (23.0%) | 175 (26.2%) | 22 (20.0%) | 160 (23.8%) |
| Grade 4, <200/mm3 | 19 (2.8%) | 12 (1.8%) | 2 (1.8%) | 20 (3.0%) |
| **Neutrophil Count** | (n=674) | (n=668) | (n=110) | (n=672) |
| Grade 3, 500 - 999/mm3 | 25 (3.7%) | 29 (4.3%) | 9 (8.2%) | 28 (4.2%) |
| Grade 4, <500/mm3 | 7 (1.0%) | 4 (0.6%) | 1 (0.9%) | 7 (1.0%) |
| **Platelet** | (n=673) | (n=668) | (n=110) | (n=671) |
| Grade 3, 25000 - 49999/mm3 | 6 (0.9%) | 6 (0.9%) | -- | 5 (0.7%) |
| Grade 4, <25000/mm3 | 4 (0.6%) | 5 (0.7%) | -- | -- |
| **Prothrombin Time (PT)** | (n=664) | (n=663) | (n=110) | (n=664) |
| Grade 3, >1.5 to 3.0 x ULN | 32 (4.8%) | 39 (5.9%) | 13 (11.8%) | 36 (5.4%) |
| Grade 4, >3.0 x ULN | 23 (3.5%) | 24 (3.6%) | 9 (8.2%) | 27 (4.1%) |
| **Partial Thromboplastin Time (PTT)** | (n=664) | (n=663) | (n=110) | (n=664) |
| Grade 3, 2.33 - 3.0 x ULN | 2 (0.3%) | 1 (0.2%) | -- | -- |
| Grade 4, >3.0 x ULN | -- | 3 (0.5%) | -- | -- |
| **White Blood Cells (WBC)** | (n=674) | (n=668) | (n=110) | (n=672) |
| Grade 3, 1000 - 1999/mm3 | 20 (3.0%) | 18 (2.7%) | 5 (4.5%) | 26 (3.9%) |
| Grade 4, <1000/mm3 | -- | -- | -- | 1 (0.1%) |

Source: Table 2.7.4.-37 of Summary of Clinical Safety; grading modified from DMID Adult Toxicity Tables 2001

Similarly, no consistent effects of belimumab were observed on electrolytes or serum chemistries (data not shown).

- **Immunogenicity**

The immunogenicity assays used for the phase 1 and 2 clinical studies were not adequate to assess immunogenicity. The phase 3 immunogenicity studies included a screening assay, an inhibition assay and a neutralization assay. A positive result in the screening assay was assessed in the inhibition assay and a positive result in the inhibition assay was assessed in the neutralization assay. A negative result in either of the first two assays resulted in no further testing. Although the phase 3 immunogenicity assays were adequately qualified and validated, in the presence of belimumab, the assays may not be able to adequately assess the real immunogenicity of belimumab. For the screening assay (an electrochemiluminescence or ECL assay), the limit of detection (LOD) for anti-drug antibodies (ADA) is 100 ng/mL in the presence of 2 µg/ml belimumab in serum. The LOD would be sufficient, except that in the presence of 40 µg/ml belimumab in serum, the LOD is 2 µg/ml ADA, indicating it would take a titer an order of magnitude higher for the assay to return positive. Similar sensitivity to the presence of belimumab in the serum was observed for the confirmation assay and the neutralizing antibody assay.

With the aforementioned caveats, immunogenicity assay results for the two pivotal studies are summarized in Table 24 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 or may be due to interference by higher concentrations of serum belimumab with the 10 mg/kg dose. The apparently higher rate of persistent immunogenicity with exposure to placebo raises questions regarding the sensitivity and specificity of the assay. 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 24: 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

- **Special safety concerns**

*Neuropsychiatric Adverse Events, Including Suicide*

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).[9] Not unexpectedly, these adverse events have been reported in the belimumab SLE clinical development program; however once again, there appears to be a numerical imbalance against belimumab, with more belimumab-treated patients reporting neurologic and psychiatric adverse events, SAEs, and suicides (Tables 25 and 26 below).

To further evaluate the potential clinical significance of the observed imbalances, the Division obtained consultation from Agency psychiatrists. In their view, the imbalance in reporting rates of psychiatric adverse events did not provide convincing evidence of a safety signal, though definitive conclusions could not be made on these limited data. The imbalance of suicides (two in the belimumab groups and none in the placebo group during the controlled period of the studies) was more concerning, but no other factors that might corroborate a relationship to belimumab were observed (e.g., dose-response or temporal clustering). In the setting of a fairly high anticipated background rate of suicidality (SLE patients reported to have a four-fold increase in risk for suicide, adjusted for observation period, age, and gender[10]), these data are even less definitive. The consultant did not believe formal analysis of the existing data using the Columbia Classification Algorithm for Suicide Assessment (C-CASA) would be productive, but did recommend consideration of the Columbia Suicide Severity Rating Scale (C-SSRS) be employed in future protocol to improve ascertainment of suicidality-related events. Nonetheless, the applicant presented results of a C-CASA analysis performed in preparation for and presented at the November 16, 2010 Advisory Committee. The applicant submitted these results to the BLA, at FDA request, on November 23, 2010.

Also, Agency psychiatrists recommended a re-analysis of anxiety-related and depression-related adverse events in the three placebo-controlled trials in which similar preferred terms are combined. For anxiety, all events were to be categorized using one of 4 preferred terms: anxiety, anxiety disorder, nervousness, and generalized anxiety disorder. For depression, all events were to be categorized using the preferred terms depressed mood, depressive symptom, depression, and major depression. The applicant submitted the requested re-analysis on December 9, 2010. No new patterns were identified; as noted in the original analysis there appeared to be slightly higher incidence of depression-related AE in the belimumab treatment groups. No consistent pattern was identified regarding anxiety-related AE.

[9] Hanly, Rheum Dis Clin N Am (2005) 31:273-298
[10] Harris and Barraclough, Medicine (1994) 73:281-296

**Table 25: 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 26: 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

*Infusion Reactions, Hypersensitivity, and Anaphylaxis*

Because belimumab is a protein for infusion that contains foreign sequences, a certain incidence 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 27, below.

**Table 27 Clinical Criteria for Diagnosing Anaphylaxis**



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 28, 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. The placebo formulation was evaluated and did not appear to be the likely cause, 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 28: Summary of Infusion Reactions, Hypersensitivity, and Anaphylaxis**

| Primary safety population (IV SLE CRD) | Belimumab 1 mg/kg N=673 N (%) | Belimumab 4 mg/kg N=111 N (%) | Belimumab 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) | 9 (1.3) | 2 (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.

- **Discussion of primary reviewer's comments and conclusions**

Dr. Neuner has concluded that the safety profile of belimumab appears to be similar to biologic products approved for other autoimmune diseases and is adequate to support approval of the BLA. Treatment with belimumab appeared to be clearly associated with an increase in infections and serious infections. Numeric imbalances (higher in belimumab treatment groups) were also observed for death, serious adverse events, and neurologic and psychiatric adverse events, including 3 suicides in belimumab-treated patients through the data cut-offs of the BLA submission. However, the magnitude of the increased risk appears to be small. No apparent increase in the risk of malignancy has been noted in the exposure experience for belimumab thus far. The reported rates of infusion reactions, hypersensitivity, and anaphylaxis do not appear to be excessive for a monoclonal antibody. I concur with Dr. Neuner's conclusions.

- **Highlight differences between CDTL and review team with explanation for CDTL's conclusion and ways that the disagreements were addressed**

Not applicable.

- **Discussion of notable safety issues (resolved or outstanding).**

Although the safety profile of belimumab appears to be characteristic of a not-particularly potent immunosuppressive, this is counterbalanced by relatively small increases in apparent

clinical efficacy, making the overall risk:benefit balance difficult to characterize. However, given the severity of the disease and the unmet medical need for additional therapeutic options in SLE, the review team believes that the safety profile of belimumab is acceptable to allow for its approval. Because of the equivocal risk:benefit balance, the review team believes that a Medication Guide is necessary to ensure the benefits of the product outweigh its risks, by ensuring patients can make an informed decision regarding whether the potential risks are acceptable. A Medication Guide had been interpreted as an element of a Risk Evaluation and Mitigation Strategy (REMS) since the passage of the Food and Drug Administration Amendments Act of 2007 (FDAAA). The applicant had not submitted a REMS with the original BLA submission, but submitted a REMS consisting of a Medication Guide, along with requested neuropsychiatric adverse event analyses, as an amendment to the BLA on November 23, 2010. However, the Agency published a draft guidance recently (end of February 2011) which clarifies that a Medication Guide may be required as labeling and in most cases will only be included as part of a REMS if the REMS includes elements to assure safe use (ETASU). Therefore the Division and OSE have concluded that the submitted REMS is no longer required, and only the Medication Guide will be brought forward for approval.

Additional post-marketing data should be required in an attempt to further characterize the risk of serious adverse events showing a numeric imbalance in the IV SLE controlled trials—i.e., mortality, serious/opportunistic infections, and depression/suicidality—and also to assess the risk of adverse events with longer latency, such as malignancy. See Section 13 for details.

# 9. Advisory Committee Meeting

A meeting of the Arthritis Advisory Committee was convened on November 16, 2010 to discuss this application. The Committee had the most questions regarding the efficacy of belimumab. These included questions about the clinical meaningfulness of the SRI endpoint, the differing efficacy between Study 1056 and Study 1057—especially in light of the fact that the more robust study was the foreign study—the apparent lack of efficacy, or even reversal of treatment effect, in patients of African extraction, and lack of data on the effect of belimumab for serious organ manifestations, such as CNS and renal disease. Nonetheless, the Committee felt that overall there was adequate evidence to support the conclusion that belimumab does have a treatment benefit, although it might be small or limited to only some patients or some manifestations. Regarding the safety of belimumab, the Committee noted the imbalances in mortality, serious infections, and neuropsychiatric adverse events but felt that the apparent extent of these risks was not unexpected and that the safety profile of belimumab overall was acceptable, even given the relatively small treatment effect size. The Committee also recommended labeling revisions to address limitations of treatment on serious organ manifestations and additional postmarketing studies in patients of African heritage and lupus nephritis.

For the three voting questions posed to the Committee, results were as follows:
1) 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?

- The Committee voted Yes, 10; No, 5; Abstentions 0. Of the 5 people voting "no," four voted no because they felt that the currently proposed labeling was too broad and needed revision. One member voted "no" because the efficacy appeared to be driven by the results of the foreign study (Study 1057).

2) 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?

- The Committee voted Yes, 14; No, 1; Abstentions 0. The consumer representative voted "no" due to the need for additional data in combination with other immunosuppressive therapies in the treatment of serious organ manifestations.

3) Do the efficacy and safety data provide substantial evidence to support approval of belimumab 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 who are receiving standard therapy?

- The Committee voted Yes, 13; No, 2; abstentions 0. Prior to this vote, it was clarified that the Committee should vote "yes" if they believed the drug should be approved for marketing, irrespective of the proposed labeling. The same member voted "no" because the efficacy appeared to be driven by the foreign study (as for question 1) and may not be generalizable to the US population. The consumer representative voted "no" because of lack of data on serious organ manifestations and the question of effects in patients of African heritage.

# 10. Pediatrics

- **Peds exclusivity board review - PPSR/WR**—not applicable
- **PeRC Review Outcome**-PMCs, deferrals, waivers, pediatric plan, peds assessment

A waiver for children under 5 was requested with the justification that studies are highly impracticable due to the rarity of the condition in this pediatric age group. A deferral for studies in pediatric lupus patients ages 5 to 17 was requested. The request for partial waiver and deferral and the proposed pediatric assessment was discussed at the Pediatric Review Committee (PeRC) meeting on October 6, 2010. The PeRC agreed with the proposed partial waiver and deferral.

The proposed pediatric study is a (b) (4)

(b) (4)

Although generally reasonable, specific Agency feedback will be provided once the final protocol is submitted.

- **Consults**—not applicable

## 11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP)**—not applicable.
- **Exclusivity or patent issues of concern**—none.
- **Financial disclosures**—submitted, no issues.
- **Other GCP issues**—not applicable.
- **DSI audits**

DSI inspection evaluated sites and protocols for Study 1056 and Study 1057. Investigator sites included Omid Zamani, M.D. (Austria), Dana Tegzova, M.D. (Czech Republic), and Chia-Li-Yu, M.D. (Taiwan). Study 1056 was conducted at 137 clinical sites, and Study 1057 was conducted at 97 clinical sites. Any given site could have been excluded without affecting overall study results, and no irregularities in results were noted. Sites were therefore selected based on larger numbers of enrollees. The inspection revealed no significant issues, therefore a Form 483 was not issued.

- **Other discipline consults**—detailed in other sections as applicable.
- **Any other outstanding regulatory issues**

The applicant had not submitted a REMS with the original BLA submission, but submitted a REMS at the Agency's request, along with requested neuropsychiatric adverse event analyses, as an amendment to the BLA on November 23, 2010. This was considered a major amendment and resulted in extension of the PDUFA date to March 10, 2011.

## 12. Labeling

- **Proprietary name**—The proposed trade name of Benlysta was reviewed by DDMAC and DMEPA and determined to be acceptable.
- **DDMAC and OSE Division comments**—Review of proposed label and Medication Guide are complete. Comments for the label are being addressed; comments for the Medication Guide have been forwarded to the applicant.
- **Physician labeling, major issues:**

- [redacted] (b) (4) Warning will be added to describe the increased risk of mortality observed in the belimumab treatment arms of the controlled periods of the randomized, controlled trials.
- Safety highlights include infections, hypersensitivity reactions including anaphylaxis, depression, and no live vaccines. Added increased mortality risk.
- Similarly, increased mortality risk was added to the full prescribing information (FPI) warnings section. FPI warnings otherwise included infections, malignancy, hypersensitivity reactions including anaphylaxis, infusion reactions, depression, and immunizations (no live vaccines, Benlysta may interfere with the response to immunizations).
- Section 6.1 Clinical Trials experience was streamlined, and readers referred back to Warnings section information.
- Added a Section 8.6 on Race, which described the lower response rates for black patients in the Benlysta group relative to black subjects in the placebo group.
- [redacted] (b) (4)
- The clinical studies section was re-arranged to separate description and results of Study LBSL02 from the Phase 3 trials. SRI results for all 3 treatment arms of each Phase 3 study are displayed in tabular format. New subsections were added on the lack of efficacy in black patients, effect of Benlysta on concomitant steroid treatment, and effect on severe SLE flares. These sections describe the negative or equivocal results for belimumab in these clinically important situations.

- **Highlight major issues that were discussed, resolved, or not resolved at the time of completion of the CDTL review**

Final labeling negotiations are pending. A labeling teleconference with the applicant was held on February 11, 2011. The primary issues that remain to be resolved include:

[redacted] (b) (4)

- **Carton and immediate container labels (if problems are noted)—** revisions/comments sent to applicant; awaiting finalization.
- **Patient labeling/Medication guide (if considered or required)—**revisions/comments sent to applicant; awaiting finalization.

# 13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

I recommend approval for the indication of "treatment of adult patients with active autoantibody-positive SLE who are receiving standard therapy," provided that agreement can be reached on revisions to the proposed label.

- **Risk Benefit Assessment**

Although there are a number of questions raised by and inconsistencies in the efficacy data submitted, substantial evidence of the efficacy of belimumab was provided by corroborating data from Trials 1056 and 1057 showing statistically significant increase in the proportion of belimumab-treated patients who were able to achieve a response as defined by the SLE Responder Index. The safety profile of belimumab appears to be consistent with that of other immunosuppressives. Given the severity of the disease and the unmet medical need for additional therapeutic options in SLE, the review team believes that the risk:benefit profile of belimumab is sufficiently commensurate to allow for its approval.

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies**

Belimumab is a biologic immunosuppressive with an increased risk of infections, hypersensitivity reactions including anaphylaxis, and infusion reactions, with the possibility of an increase rate of death and depression/suicidality, as well. Therefore, the review team believes a Medication Guide is warranted. As mentioned above in Section 8, a Medication Guide was interpreted as requiring a REMS until recent guidance to the contrary. Therefore the applicant's submitted REMS will not be finalized, but the Medication Guide will be finalized as part of labeling.

- **Recommendation for other Postmarketing Requirements and Commitments**

Clinical Postmarketing Requirements:

1) Randomized, controlled safety study to further evaluate adverse events of special interest, such as mortality, malignancy, serious and opportunistic infections, and depression/suicidality.
   - Final protocol submission: September 2011
   - Study completion: 1-year, May 2018; 2-year, May 2019, 5-year, May 2022
   - Final report submission: May 2023 (5-year data).

The applicant has proposed a 5000 patient study (2500 patients per group) (b) (4)
r

(b) (4)

(b) (4)

It is likely impractical to require a larger study due to the limited patient population available for such a study. Therefore practical considerations may reasonably limit the power of the study and the relative risk that can be ruled out for the AEs of interest. Although the applicant's proposal preliminarily seems reasonable, the details of the protocol have yet to be finalized.

2) Pregnancy registry
- Final protocol submission: July 2011
- Study completion date: October 2018
- Final report submission: April 2019

3) PREA-required pediatric study
- Final protocol submission: August 2011
- Study Completion: March 2016
- Final report submission: October 2016 (excluding long-term follow up)

4) Vaccination study
Because belimumab affects B-cells and may interfere with host responses to vaccination, the applicant proposed a controlled vaccination study to better characterize any impairment of responses.

- Final protocol submission: December 2011
- Study completion: March 2014
- Final report submission: September 2014

Clinical Postmarketing Commitments:

1) Lupus Nephritis study
As mentioned by the Arthritis Advisory Committee, the efficacy of belimumab on this important manifestation should be further evaluated, and the applicant has agreed to conduct a pilot study.

- Final protocol submission: January 2012
- Trial completion (through end of controlled period): January 2017
- Final report submission (through end of controlled period): October 2017

2) Patients of Black Race study
Also discussed at the Advisory Committee meeting, the effect of belimumab on patients of Black race needs to be further evaluated, given the negative results in Trials 1056 and 1057 and the importance of this subpopulation of US SLE patients.

- Final protocol submission: November 2011
- Study completion: July 2017
- Final report submission: January 2018.

3) Submit a final study report for long-term open-label continuation study LBSL99

- Study completion: May 2016
- Final report submission December 2016

4) Submit a final study report for long-term open-label continuation study C1066

- Study completion: May 2015
- Final report submission: December 2015

5) Submit a final study report for long-term open-label continuation study C1074

- Study completion: March 2015
- Final report submission: October 2015

For the single CMC postmarketing requirement and 3 CMC postmarketing commitments, see Section 3.

- **Recommended Comments to Applicant**

None.